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(54) **7-(Substituted)-9- (substituted glycyl)-amido)-6-demethyl-6-deoxytetracyclines**

7-Substituierte-9-substituierte Glycylamido-6-Demethyl-6-Deoxytetracycline

6-démétyl-6-déoxy-tétracyclines substituées en position 7 et en position 9 par un groupe glycyl-amido substitué

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US-A- 3 338 963

- **JOURNAL OF MEDICINAL CHEMISTRY vol. 6, no. 4, July 1963, WASHINGTON US pages 405 - 407 JOHN L. SPENCER ET AL. '6-Deoxytetracyclines. V. 7,9-Disubstituted Products'**

Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

EP 0 582 788 B1

Description

BACKGROUND OF THE INVENTION

1. Field of the Invention

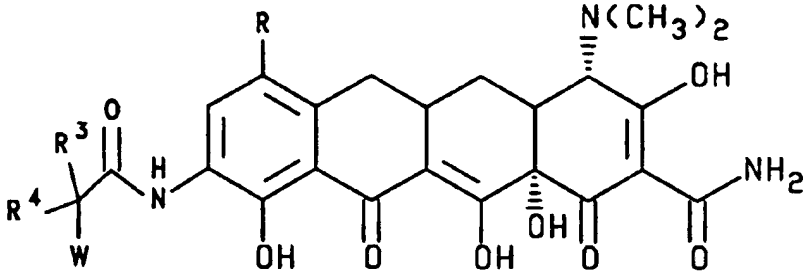
The invention relates to novel [4S-(4alpha, 12aalpha)]-4-(dimethylamino)-7-(substituted)-9-[(substituted glycyl) amido]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamides herein after called 7-(substituted)-9-[(substituted glycyl)amido]-6-demethyl-6-deoxytetracyclines, which exhibit antibiotic activity against a wide spectrum of organisms including organisms which are resistant to tetracyclines and are useful as antibiotic agents.

The invention also relates to novel 9-[(haloacyl)amido]-7-(substituted)-6-demethyl-6-deoxytetracycline intermediates useful for making the novel compounds of the present invention and to novel methods for producing the novel compounds and intermediate compounds.

EP Publication No 536515 (published 14 April 1993) discloses certain novel 7-substituted-9-substituent amino-6-demethyl-6-deoxytetracyclines included those where the 9-position is substituted by acetylamino which is itself substituted by benzylamino, piperidinyl, 1-imidazolyl, pyrrolyl, (1-(1,2,3-triazolyl) and 4-(1,2,4-triazolyl).

SUMMARY OF THE INVENTION

This invention is concerned with novel 7-(substituted)-9-[(substituted glycyl)amido]-6-demethyl-6-deoxytetracyclines, represented by formula I and II, which have antibacterial activity; with methods of treating infectious diseases in warm blooded animals employing these new compounds; with pharmaceutical preparations containing these compounds; with novel intermediates compounds and processes for the production of these compounds. More particularly, this invention is concerned with compounds of formula I and II which have enhanced antibacterial activity against tetracycline reisitant strains as well as a high level of activity against strains which are normally susceptible to tetracyclines.



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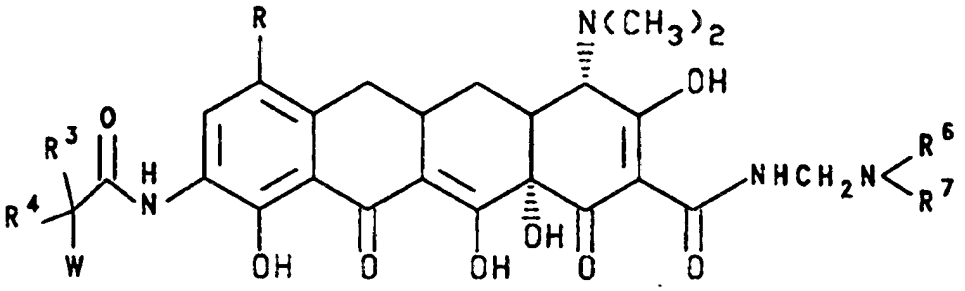


II

In formula I and II,

R is a halogen selected from bromine, chlorine, fluorine and iodine; or R – $-NR^1R^2$ and when R – $-NR^1R^2$ and R^1 – hydrogen,

R^2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl; and when R^1 – methyl or ethyl.

R^2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R^1 = n-propyl,

R^2 = n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R^1 = 1-methylethyl,

R^2 = n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R^1 = n-butyl,

R^2 = n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R^1 – 1-methylpropyl,

R^2 = 2-methylpropyl;

R^3 is selected from hydrogen; straight or branched (C_4-C_8)alkyl group selected from butyl, isobutyl, pentyl, hexyl, heptyl and octyl;

α-mercapto(C_1-C_4)alkyl group selected from mercaptomethyl, α-mercaptoethyl, α-mercapto-1-methylethyl and α-mercaptopropyl,

α-hydroxy(C_1-C_4)alkyl group selected from hydroxymethyl, α-hydroxyethyl, α-hydroxy-1-methylethyl and α-hydroxypropyl; carboxyl(C_1-C_8)alkyl group;

(C_6-C_{10})aryl group selected from phenyl, α-naphthyl and β-naphthyl, substituted(C_6-C_{10})aryl group (substitution selected from hydroxy, halogen, (C_1-C_4)alkoxy,

trihalo(C_1-C_3)alkyl, nitro, amino, cyano,

(C_1-C_4)alkoxycarbonyl, (C_1-C_3)alkylamino and carboxy);

(C_7-C_9)aralkyl group selected from benzyl,

1-phenylethyl, 2-phenylethyl and phenylpropyl;

substituted (C_7-C_9)aralkyl group [substitution selected from halo, (C_1-C_4)alkyl, nitro, hydroxy, amino, mono-or disubstituted (C_1-C_4)alkylamino (C_1-C_4)alkoxy, (C_1--C_4)alkylsulfonyl, cyano and carboxy];

R^4 is selected from hydrogen and (C_1-C_6)alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl;

when R^3 does not equal R^4 the stereochemistry of the asymmetric carbon (i.e the carbon bearing the substituent W) maybe be either the racemate (DL) or the individual enantiomers (L or D);

W is selected from hydroxylamino; (C_7-C_{12}) straight or branched alkyl monosubstituted amino group substitution selected from heptyl, octyl, nonyl, decyl, undecyl, dodecyl and the diastereomers and enantiomers of said branched alkyl monosubstituted amino group. (C_1-C_4) straight or branched fluoroalkylamino group selected from trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, 3,3,3,2,2-pentafluoropropyl, 2,2-difluoropropyl, 4,4,4-trifluorobutyl and 3,3-difluorobutyl; [(C_4-C_{10})cycloalkyl]alkyl monosubstituted amino group substitution selected from (cyclopropyl)methyl, (cyclopropyl)ethyl, (cyclobutyl)methyl, (trans-2-methylcyclopropyl)methyl, and (cis-2-methylcyclobutyl)methyl; (C_3-C_{10}) alkenyl and alkynyl monosubstituted amino group substitution selected from allyl, 3-butenyl, 2-butenyl (cis or trans) 2-pentenyl, propynyl, 4-octenyl, 2,3-dimethyl-2-butenyl, 3-methyl-2-butenyl, 2-cyclopentenyl and 2-cyclohexenyl; (C_7-C_{10})aralkylamino group substitution selected from benzyl, 2-phenylethyl, 1-phenylethyl, 2-(naphthyl)methyl, 1-(naphthyl)methyl and phenylpropyl substituted (C_6-C_{10})aryl monosubstituted amino group [substitution selected from

(C_1-C_5)acyl, (C_1-C_5)acylamino, (C_1-C_4)alkyl, mono or disubstituted (C_1-C_8)alkylamino, (C_1-C_4)alkoxy, (C_1-C_4)alkoxycarbonyl, (C_1-C_4)alkylsulfonyl, amino, carboxy, cyano, halogen, hydroxy, nitro and trihalo(C_1-C_3)alkyl];

straight or branched symmetrical disubstituted alkylamino group substitution selected from dibutyl, diisobutyl, di-sec-butyl, dipentyl, diisopentyl, di-sec-pentyl, dihexyl, diisohexyl and di-sec-hexyl; symmetrical disubstituted (C_6-C_{14})cycloalkylamino group substitution selected from dicyclopropyl, dicyclobutyl, dicyclopentyl, di(dicyclopropyl)methyl, dicyclohexyl and dicycloheptyl;

straight or branched unsymmetrical disubstituted (C_3-C_{14})alkylamino group wherein the total number of carbons in the substitution is more than 14; unsymmetrical disubstituted (C_4-C_{14})cycloalkylamino group wherein the total number of carbons in the substitution is no more than 14;

(C_2-C_8)azacycloalkyl and substituted (C_2-C_8)azacyclo-alkyl group substitution selected from 4-methylpiperidinyl, 4-hydroxypiperidinyl, 4-(hydroxymethyl)piperidinyl, 4-(aminomethyl)piperidinyl, cis-3,4-dimethylpyrrolidinyl, trans-3,4-dimethylpyrrolidinyl, 2-azabicyclo [2.1.1]hex-2-yl, 5-azabicyclo[2.1.1]hex-5-yl, 2-azabicyclo[2.2.1]hept-2-yl, 7-azabicyclo[2.2.1]-hept-7-yl, 2-azabicyclo[2.2.2]oct-2-yl and the diastereomers and enantiomers of said (C_2-C_8)azacycloalkyl and substituted (C_2-C_8)azacycloalkyl group; substituted 1-azaoxacycloalkyl group substitution selected from 2-(C_1-C_3)alkylmorpholinyl, 3-(C_1-C_3)alkylisoxazolidinyl, tetrahydrooxazinyl and 3,4-dihydrooxazinyl; [1,n]-diazacycloalkyl and

substituted [1,n]-diazacycloalkyl group selected from piperazinyl, 2-(C_1-C_3)alkylpiperazinyl, 4-(C_1-C_3)alkylpiperazinyl, 2,4-dimethylpiperazinyl, 4-(C_1-C_4)alkoxypiperazinyl, 4-(C_6-C_{10})aryloxypiperazinyl, 4-hydroxypiperazinyl, 2,5-diazabicyclo[2.2.1]hept-2-yl, 2,5-diaza-5-methylbicyclo[2.2.1]hept-2-yl, 2,3-diaza-3-methylbicyclo[2.2.2]oct-2-yl, 2,5-diaza-5,7-dimethylbicyclo[2.2.2]oct-2-yl and the diastereomers or enantiomers of said [1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group; 1-azathiacycloalkyl and substituted 1-azathiacycloalkyl group selected from thiamorpholinyl, 2-(C_1-C_3)alkyl-thiomorpholinyl and 3-(C_3-C_6)cycloalkylthiomorpholinyl; N-azolyl and substituted N-azolyl group selected from 1-imidazolyl, 2-(C_1-C_3)alkyl-1-imidazolyl, 3-(C_1-C_3)alkyl-1-imidazolyl, 1-pyrrolyl, 2-(C_1-C_3)-alkyl-1-pyrrolyl, 3-(C_1-C_3)alkyl-1-pyrrolyl, 1-pyrazolyl, 3-(C_1-C_3)alkyl-1-pyrazolyl, indolyl, 1-(1,2,3-triazolyl), 4-(C_1-C_3)alkyl-1-(1,2,3-triazolyl), 5-(C_1-C_3)alkyl-1-(1,2,3-triazolyl), 4-(1,2,4-triazolyl, 1-tetrazolyl, 2-tetrazolyl and benzimidazolyl; (heterocycle)amino group said heterocycle selected from 2- or 3-furanyl, 2- or 3-thienyl, 2-, 3- or 4-pyridyl, 2- or 5-pyridazinyl, 2-pyrazinyl, 2-(imidazolyl), (benzimidazolyl), and (benzothiazolyl) and substituted (heterocycle)amino group (substitution selected from straight or branched (C_1-C_6)alkyl), (heterocycle)methylamino group selected from 2- or 3-furylmethylamino, 2- or 3-thienylmethyl-amino, 2-, 3- or 4-pyridylmethylamino, 2- or 5-pyridazinylmethylamino, 2-pyrazinylmethylamino, 2-(imidazolyl)methylamino, (benzimidazolyl)methylamino, and (benzothiazolyl)methylamino and said substituted (heterocycle)methylamino group (substitution selected from straight or branched (C_1-C_6)alkyl); carboxy (C_2-C_4)-alkylamino group selected from aminoacetic acid, α-aminopropionic acid, β-aminopropionic acid, α-aminobutyric acid, β-aminobutyric acid and the enantiomers of said carboxy(C_2-C_4)alkylamino group; 1,1-disubstituted hydrazino group selected from 1,1-dimethylhydrazino, N-aminopiperidinyl, 1,1-diethylhydrazino, and N-aminopyrroli- dinyl;

(C_1-C_4)alkoxyamino group substitution selected from methoxy, ethoxy, n-propoxy, 1-methylethoxy, n-butoxy, 2-methylpropoxy and 1,1-dimethylethoxy; (C_3-C_8)cycloalkoxyamino group selected from cyclopropoxy, trans-1,2-dimethylcyclopropoxy, cis-1,2-dimethylcyclopropoxy, cyclobutoxy, cyclopentoxy, cyclohexoxy, cycloheptoxy, cyclooctoxy, bicyclo [2.2.1]hept-2-yloxy, bicyclo[2.2.2]oct-2-yloxy and the diastereomers and enantiomers of said (C_3-C_8)cycloalkoxyamino group;

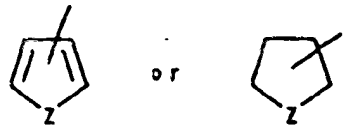
(C_6-C_{10})aryloxyamino group selected from phenoxyamino, 1-naphthyloxyamino and 2-naphthyloxyamino;

(C_7-C_{11})arylalkoxyamino group substitution selected from benzyloxy, 2-phenylethoxy, 1-phenylethoxy, 2-(naphthyl) methoxy, 1-(naphthyl)methoxy and phenylpropoxy;

[β or γ-C_1-C_3)acylamido)alkylamino group substitution selected from 2-(formamido)ethyl, 2-(acetamido)ethyl, 2-(propionylamido)ethyl, 2-(acetamido)propyl, 2-(formamido)propyl and the enantiomers of said [β or γ-(C_1-C_3)acylamido] alkylamino group, β or γ-(C_1-C_3)alkoxyalkylamino group substitution selected from 2-methoxyethyl, 2-ethoxyethyl, 2,2-diethoxyethyl, 2-methoxypropyl, 3-methoxypropyl, 3-ethoxypropyl, 3,3-diethoxypropyl and the enantiomers of said β or γ-(C_1-C_3)alkoxyalkylamino group; β, γ, or δ (C_2-C_4)hydroxyalkylamino group substitution selected from 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl and 4-hydroxybutyl;

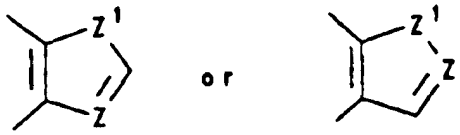
or R^3 and W taken together are selected from -$(CH_2)_n(R^5)$N-, n= 3 - 4, and -$CH_2CH(OH)CH_2(R^5)$N- wherein R^5 is selected from hydrogen and (C_1-C_3)acyl, the acyl selected from formyl, acetyl, propionyl and (C_2-C_3)haloacyl selected from chloroacetyl, bromoacetyl, trifluoroacetyl, 3,3,3-trifluoropropionyl and 2,3,3-trifluoropropionyl;

R^6 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (C_6-C_{10})aryl group selected from phenyl, α-naphthyl or β-naphthyl; (C_7-C_9)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:



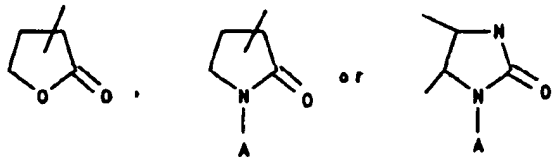
Z - N, O, S or Se

such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:



Z or Z^1 - N, O, S or Se

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazo[4,5-b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:

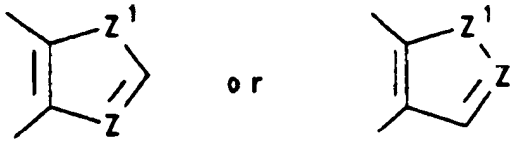


(A is selected from hydrogen; straight or branched (C_1-C_4)alkyl; C_6-aryl; substituted C_6-aryl (substitution selected from halo,(C_1-C_4)alkoxy, trihalo(C_1-C_3)alkyl, nitro, amino, cyano, (C_1-C_4)-alkoxycarbonyl, (C_1-C_3)alkylamino or carboxy); (C_7-C_9)-aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)

such as γ-butyrolactam, γ-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, sym-triazinyl, unsym-triazinyl, pyrimidinyl or (C_1-C_3) alkylthiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1-piperazinyl, 2-dioxomorpholinyl, 2-dioxothiomorpholinyl; or $-(CH_2)_nCOOR^8$ where n=0-4 and R^8 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; or (C_6-C_{10})aryl group selected from phenyl, α-naphthyl, or β-naphthyl; R^7 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (C_6-C_{10})aryl group selected from phenyl, α-naphthyl or β-naphthyl, (C_7-C_9)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

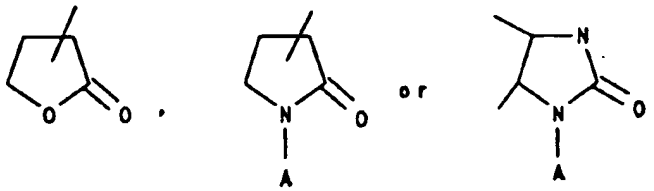
Z = N, O, S or Se

such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:



Z or Z^1 = N, O, S or Se

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazo[4.5-b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



(A is selected from hydrogen; straight or branched (C_1-C_4)alkyl; C_6-aryl; substituted C_6-aryl (substitution selected from halo,(C_1-C_4)alkoxy, trihalo(C_1-C_3)alkyl, nitro, amino, cyano, (C_1-C_4)-alkoxycarbonyl, (C_1-C_3)alkylamino or carboxy); (C_7-C_9)-aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)
such as γ-butyrolactam, γ-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, sym-triazinyl, unsym-triazinyl, pyrimidinyl or (C_1-C_3)alkylthiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1-piperazinyl, 2-dioxomorpholinyl, 2-dioxothiomorpholinyl; or $-(CH_2)_nCOOR^8$ where n=0-4 and R^8 is selected from hydrogen; straight or branched (C_1-C_3)alkyl selected from methyl, ethyl, n-propyl or 1-methylethyl; or (C_6-C_{10})aryl selected from phenyl, α-naphthyl or β-naphthyl, with the proviso that R^6 and R^7 cannot both be hydrogen;
or R^6 and R^7 taken together are $-(CH_2)_2B(CH_2)_2-$, wherein B is selected from $(CH_2)n$ and n=0-1, -NH, $-N(C_1$-$C_3)$alkyl [straight or branched], $-N(C_1$-$C_4)$alkoxy, oxygen, sulfur or substituted congeners selected from (L or D)proline, ethyl(L or D)prolinate, morpholino, pyrrolidino or piperidino; and the pharmacologically acceptable organic and inorganic salts or metal complexes, with the proviso that when R^3 and R^4 both represent hydrogen then W is other than benzylamino, 1-midazolyl, 1-pyrrolyl, 1-(1,2,3-triazolyl) or 4-(1 2 4-triazolyl).

Preferred compounds are compounds according to the above formula I and II wherein:
R is a halogen selected from bromine, chlorine, fluorine and iodine, or R = $-NR^1R^2$ and when R = $-NR^1R^2$ and R^1 = hydrogen, R^2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;

and when R^1 methyl or ethyl, R^2 methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl; R^3 is selected from hydrogen; straight or branched (C_4-C_8)alkyl group selected from butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α-hydroxy(C_1-C_4)alkyl group selected from hydroxymethyl, α-hydroxyethyl, α-hydroxy-1-methylethyl and α-hydroxypropyl; carboxyl(C_1-C_8)alkyl group; (C_6-C_{10})aryl group selected from phenyl, α-naphthyl and β-naphthyl; substituted (C_6-C_{10})aryl group (substitution selected from hydroxy, halogen, (C_1-C_4)alkoxy, (C_1-C_4)alkoxycarbonyl and carboxy); (C_7-C_9)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl; substituted (C_7-C_9)aralkyl group [substitution selected from halo (C_1-C_4)alkyl, (C_1-C_4)alkoxy (C_1-C_4)alkylsulfonyl, cyano and carboxy]; R^4 is selected from hydrogen and (C_1-C_4)alkyl selected from methyl, ethyl, propyl, isopropyl, butyl and isobutyl;

when R^3 does not equal R^4 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the substituent W) maybe be either the racemate (DL) or the individual enantiomers (L or D);

W is selected from hydroxylamino; (C_7-C_{12}) straight or branched alkyl monosubstituted amino group substitution selected from heptyl, octyl, nonyl, decyl, undecyl, dodecyl and the diastereomers and enantiomers of said branched alkyl monosubstituted amino group;

(C_1-C_4) straight or branched fluoroalkylamino group selected from 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, 2,2-difluoropropyl and 3,3-difluorobutyl; [(C_4-C_{10})cycloalkyl]-alkyl monosubstituted amino group substitution selected from (cyclopropyl)methyl, (cyclopropyl)ethyl, (cyclobutyl)methyl, (trans-2-methylcyclopropyl)methyl, and (cis-2-methylcyclobutyl)methyl; (C_3-C_{10})alkenyl and alkynyl monosubstituted amino group substitution selected from allyl, 3-butenyl, 2-butenyl (cis or trans), 2-pentenyl, propynyl, 4-octenyl, 2,3-dimethyl-2-butenyl and 3-methyl-2-butenyl; (C_7-C_{10})aralkylamino group substitution selected from benzyl, 2-phenylethyl, 1-phenylethyl, 2-(naphthyl)methyl, 1-(naphthyl)methyl and phenylpropyl; straight or branched symmetrical disubstituted alkylamino group substitution selected from dibutyl, diisobutyl, di-s-butyl dipentyl diisopentyl and di-s-pentyl; symmetrical disubstituted (C_6-C_{14})cycloalkylamino group substitution selected from dicyclopropyl, dicyclobutyl, dicyclopentyl and di(dicyclopropyl)methyl; straight or branched unsymmetrical disubstituted (C_3-C_{14})alkylamino group wherein the total number of carbons in the substitution is no more than 14; unsymmetrical disubstituted (C_4-C_{14})cycloalkylamino group wherein the total number of carbons in the substitution is no more than 14; (C_2-C_8)azacycloalkyl and substituted (C_2-C_8)azacycloalkyl group substitution selected from 4-methylpiperidinyl, 4-hydroxypiperidinyl, 4-(hydroxymethyl)piperidinyl, 4-(aminomethyl)piperidinyl, cis-3,4-dimethylpyrrolidinyl, trans-3,4-dimethylpyrrolidinyl, 2-azabicyclo [2.2.1]hept-2-yl, 7-azabicyclo-[2.2.1]hept-7-yl, 2-azabicyclo[2.2.2]oct-2-yl and the diastereomers and enantiomers of said (C_2-C_8)azacycloalkyl and substituted (C_2-C_8)azacycloalkyl and substituted (C_2-C_8)azacycloalkyl group;

substituted 1-azaoxacycloalkyl group substitution selected from 2-(C_1-C_3)alkylmorpholinyl, 3-(C_1-C_3)alkylisoxazolidinyl and tetrahydrooxazinyl;

[1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group selected from piperazinyl, 2-2-(C_1-C_3)alkylpiperazinyl, 4-(C_1-C_3)alkylpiperazinyl, 2,4-dimethylpiperazinyl, 4-(C_1-C_4)-alkoxypiperazinyl, 4-(C_6-C_{10})aryloxypiperazinyl, 4-hydroxypiperazinyl, 2,3-diaza-3-methylbicyclo[2.2.2]oct-2-yl, 2,5-diaza-5,7dimethylbicyclo[2.2.2]oct-2-yl, -2-yl and the diastereomers or enantiomers of said [1,n]-diazacycloalkyl and substituted [1,n]-di- azacycloalkyl group;

1-azathiacycloalkyl and substituted 1-azathiacycloalkyl group selected from thiomorpholinyl, 2-(C_1-C_3)alkylthiomorpholinyl and 3-(C_3-C_6)cycloalkylthiomorpholinyl;

N-azolyl and substituted N-azolyl group selected from 1-imidazolyl, 1-pyrrolyl, 1-pyrazolyl, 3-(C_1-C_3)alkylpyrazolyl, indolyl, 1-(1,2,3-triazolyl), 4-(1,2,4-triazolyl), 1-tetrazolyl, 2-tetrazolyl and benzimidazolyl;

(heterocycle)methylamino group selected from 2- or 3-furylmethylamino, 2- or 3-thienylmethylamino, 2-, 3- or 4-pyridylmethylamino, 2- or 5-pyridazinylmethylamino, 2-pyrazinylmethylamino, 2-(imidazolyl)methylamino, (benzimidazolyl)methylamino, and (benzothiazolyl)methylamino and substituted (heterocycle)methylamino group (substitution selected from straight or branched (C_1-C_6)alkyl); carboxy(C_2-C_4)alkylamino group selected from aminoacetic acid, α-aminopropionic acid, β-aminopropionic acid, α-butyric acid, and β-aminobutyric acid and the enantiomers of said carboxy(C_2-C_4)alkylamino group; 1,1-disubstituted hydrazino group selected from 1,1-dimethylhydrazino, N-aminopiperidinyl and 1,1-diethylhydrazino;

(C_1-C_4)alkoxyamino group substitution selected from methoxy, ethoxy, n-propoxy, 1-methylethoxy, n-butoxy, 2-methylpropoxy and 1,1-dimethylethoxy;

(C_3-C_8)cycloalkoxyamino group selected from cyclopropoxy, trans-1,2-dimethylcyclopropoxy, cis-1,2-dimethylcyclopropoxy, cyclobutoxy, and the diastereomers and enantiomers of said (C_3-C_8)cycloalkoxyamino group;

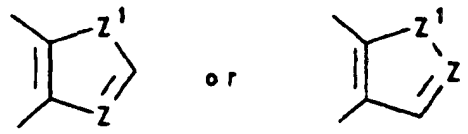
(C_6-C_{10})aryloxyamino group selected from phenoxyamino, 1-naphthyloxyamino and 2-naphthyloxyamino;

(C_7-C_{11})arylalkoxyamino group substitution selected from benzyloxy, 2-phenylethoxy, 1-phenylethoxy, 2-(naphthyl)methoxy, 1-(naphthyl)methoxy and phenylpropoxy; [β or γ-(C_1-C_3)acylamido]alkylamino group substitution selected from 2-(formamido)ethyl, 2-(acetamido)ethyl, 2-(propionylamido)ethyl, 2-(acetamido)propyl, 2-(formamido)propyl and the enantiomers of said [β or γ-(C_1-C_3)acylamido]alkylamino group; β or γ-(C_1-C_3)alkoxyalkylamino group substitution selected from 2-methoxyethyl, 2-ethoxyethyl, 2,2-diethoxyethyl, 2-methoxypropyl, 3-methoxypropyl, 3-ethoxypropyl, 3,3-diethoxypropyl and the enantiomers of said β or γ-(C_1-C_3)alkoxyalkylamino group; β, γ or δ (C_2-C_4) hydroxyalkylami-

no group substitution selected from 2-hydroxyethyl, 3-hydroxypropyl, and 4-hydroxybutyl;
or R^6 and W taken together are selected from $-(CH_2)_n(R^5)N-$, n= 3 - 4, and $-CH_2CH(OH)CH_2(R^5)N-$ wherein R^5 is selected from hydrogen and (C_1-C_3)acyl, the acyl selected from formyl, acetyl, propionyl and (C_2-C_3)haloacyl selected from chloroacetyl, bromoacetyl, trifluoroacetyl, 3,3,3-trifluoropropionyl and 2,3,3-trifluoropropionyl;
R^6 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (C_6-C_{10})aryl group selected from phenyl, α-naphthyl or β-naphthyl; (C_7-C_9)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

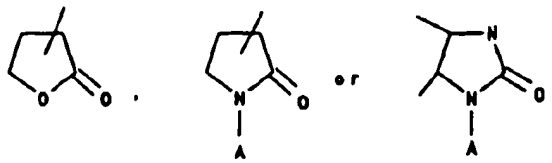
Z = N, O, S or Se

such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:



Z or Z^1 = N, O, S or Se

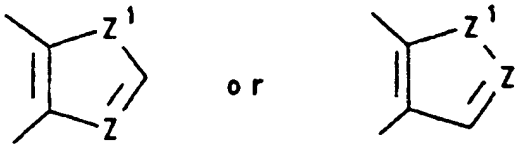
such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazo[4,5-b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



(A is selected from hydrogen; straight or branched (C_1-C_4)alkyl; C_6-aryl; (C_7-C_9)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)
such as γ-butyrolactam, γ-butyrolactone, imidazolidinone or N-aminoimidazolidinone; or $-(CH_2)_nCOOR^5$ where n=0-4 and R^8 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl;
or (C_6-C_{10})aryl group selected from phenyl, α-naphthyl, or β-naphthyl.
R^7 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (C_6-C_{10})aryl group selected from phenyl, α-naphthyl or β-naphthyl; (C_7-C_9)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

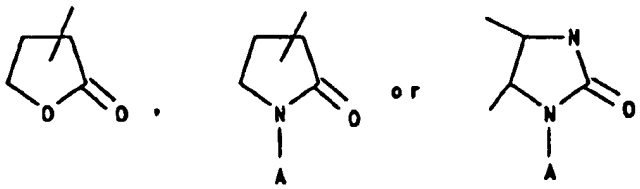
Z = N, O, S or Se

such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:



Z or Z^1 = N, O, S or Se

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazo[4.5-b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



(A is selected from hydrogen; straight or branched (C_1-C_4)alkyl; C_6-aryl; (C_7-C_9)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)
such as γ-butyrolactam, γ-butyrolactone, imidazolidinone or N-aminoimidazolidinone; or $-(CH_2)_nCOOR^8$ where n=0-4 and R^8 is selected from hydrogen; straight or branched (C_1-C_3)alkyl selected from methyl, ethyl, n-propyl or 1-methylethyl; or (C_6-C_{10})aryl selected from phenyl, α-naphthyl or β-naphthyl; with the proviso that R^6 and R^7 cannot both be hydrogen;
or R^6 and R^7 taken together are $-(CH_2)_2B(CH_2)_2-$, wherein B is selected from $(CH_2)_n$ and n=0-1, -NH, $-N(C_1$-$C_3)$alkyl [straight or branched], $-N(C_1$-$C_4)$alkoxy, oxygen, sulfur or substituted congeners selected from (L or D)proline, ethyl(L or D)prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts or metal complexes.

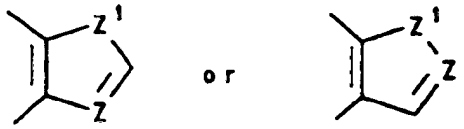
Particularly preferred compounds are compounds according to formula I and II wherein:
R is a halogen selected from bromine, chlorine, fluorine and iodine, or R = $-NR^1R^2$ and when R = $-NR^1R^2$ and R^1 = hydrogen,
R^2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;
and when R^1 = methyl or ethyl,
R^2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;
R^3 is selected from hydrogen; straight or branched (C_4–C_6)alkyl group selected from butyl, isobutyl, pentyl and hexyl; (C_6-C_{10})aryl group selected from phenyl, α-naphthyl and β-naphthyl; (C_7-C_9)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl;

R^4 is selected from hydrogen and (C_1-C_3)alkyl selected from methyl, ethyl, propyl and isopropyl;
when R^6 does not equal R^4 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the substituent W) maybe be either the racemate (DL) or the individual enantiomers (L or D);
W is selected from (C_7-C_{12}) straight or branched alkyl monosubstituted amino group substitution selected from heptyl, octyl, nonyl, decyl, undecyl, dodecyl and the diastereomers and enantiomers of said branched alkyl monosubstituted amino group; (C_1-C_4) straight or branched fluoroalkylamino group selected from 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl and 2,2-di-fluoropropyl;
[(C_4-C_{10})cycloalkyl]alkyl monosubstituted amino group substitution selected from (cyclopropyl)methyl, (cyclopropyl) ethyl and (cyclobutyl)methyl; (C_3-C_{10})alkenyl and alkynyl monosubstituted amino group substitution selected from allyl, propynyl, 3-butenyl, 2-butenyl (cis or trans) and 2-pentenyl; (C_7-C_{10})aralkylamino group substitution selected from benzyl, 2-phenylethyl, 1-phenylethyl, 2-(naphthyl)methyl, 1-(naphthyl)methyl and phenylpropyl, straight or branched symmetrical disubstituted alkylamino group substitution selected from dibutyl, diisobutyl, di-s-butyl, and dipentyl; symmetrical disubstituted (C_6-C_{14})cyclo-alkylamino group substitution selected from dicyclopropyl, dicyclobutyl, dicyclopentyl and dicyclopropylmethyl; straight or branched unsymmetrical disubstituted (C_3-C_{14})alkylamino group wherein the total number of carbons in the substitution is no more than 14; unsymmetrical disubstituted (C_4-C_{14})cycloalkylamino group wherein the total number of carbons in the substitution is no more than 14; (C_2-C_8)azacycloalkyl and substituted (C_2-C_8)azacycloalkyl group substitution selected from 4-methylpiperidinyl, 4-hydroxypiperidinyl, 4-(hydroxymethyl)-piperidinyl, 4-(aminomethyl)piperidinyl, cis-3,4-dimethylpyrrolidinyl, trans-3,4-dimethylpyrrolidinyl and the diastereomers and enantiomers of said (C_2-C_8)azacycloalkyl and substituted (C_2-C_8)azacycloalkyl group; substituted 1-azaoxacycloalkyl group substitution selected from 2-(C_1-C_3)alkylmorpholinyl and 3-(C_1-C_3)alkylisoxazolidinyl; [1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group selected from piperazinyl, 2-(C_1-C_3)alkylpiperazinyl, 4-(C_1-C_3)-alkylpiperazinyl, 2,4-dimethylpiperazinyl, 4-hydroxypiperazinyl, and the enantiomers of said [1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group; 1-azathiacycloalkyl and substituted 1-azathiacycloalkyl group selected from thiomorpholinyl and 2-(C_1-C_3)alkylthiomorpholinyl;
(heterocyclo)methylamino group selected from 2- or 3-furylmethylamino, 2- or 3-thienylmethylamino, 2-, 3-or 4-pyridylmethylamino, 2- or 5-pyridazinylmethyl 2-pyrazinylmethylamino, 2-(imidazolyl)methylamino and the substituted (heterocycle)methylaminno group (substitution selected from straight or branched (C_1-C_6)alkyl); 1,1-disubstituted hydrazino group selected from 1,1-dimethylhydrazino, N-aminopiperidinyl and 1,1-diethylhydrazino;
(C_1-C_4)alkoxyamino group substitution selected from methoxy, ethoxy, n-propoxy, 1-methylethoxy, n-butoxy, 2-methylpropoxy and 1,1-dimethylethoxy;
(C_7-C_{11})arylalkoxyamino group substitution selected from benzyloxy, 2-phenylethoxy, 1-phenylethoxy, 2-(naphthyl) methoxy, 1-(naphthyl)methoxy and phenylpropoxy;
[β or γ-(C_1-C_3)acylamido]alkylamino group substitution selected from 2-(formamido)ethyl, 2-(acetamido)ethyl, 2-(propionylamido)ethyl, 2-(acetamido)propyl and 2-(formamido)propyl and the enantiomers of said [β or γ-(C_1-C_3)acylamido] alkylamino group;
β or γ-(C_1-C_3)alkoxyalkylamino group substitution selected from 2-methoxyethyl, 2-ethoxyhyl, 2,2-diethoxyethyl, 2-methoxypropyl, 3-methoxyopyl, 3-ethoxypropyl and 3,3-diethoxypropyl and the enantiomers of said β or γ-(C_1-C_3) alkoxyalkyl- amino group; β, γ or δ (C_2-C_4) hydroxyalkylamino group selected from 3-hydroxypropyl and 4-hydroxybutyl; or R^3 and W taken together are selected from -$(CH_2)_n(R^5)N$-, n= 3 - 4, and -$CH_2CH(OH)CH_2(R^5)N$- wherein R^5 is selected from hydrogen and (C_1-C_3)acyl, the acyl selected from formyl, acetyl, propionyl and (C_2-C_3)haloacyl selected from trifluoroacetyl, 3,3,3-trifluoropropionyl and 2,3,3-trifluoropropionyl;
R^6 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (C_6-C_{10})aryl group selected from phenyl, α-naphthyl or β-naphthyl; (C_7-C_9)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

Z - N, O, S or Se

such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl or a five membered aromatic ring with two N, O, S or

Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

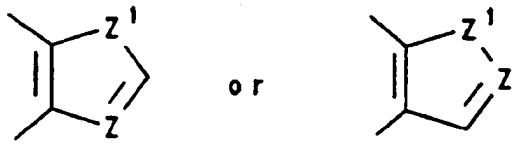


Z or Z¹ - N, O, S or Se

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazo[4,5-b]pyridyl or pyridylimidazolyl; or $-(CH_2)_nCOOR^8$ where n=0-4 and R^8 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; or (C_6-C_{10})aryl group selected from phenyl, α-naphthyl, or β-naphthyl;
R^7 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (C_6-C_{10})aryl group selected from phenyl α-naphthyl or β-naphthyl; (C_7-C_9)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

Z - N, O, S or Se

such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl; or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:



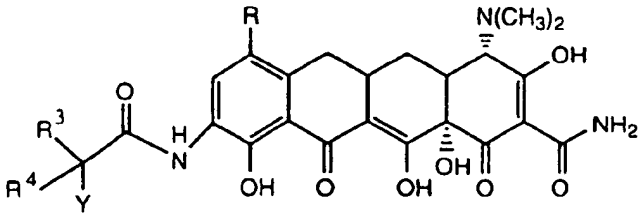
Z or Z¹ - N, O, S or Se

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazo[4,5-b]pyridyl or pyridylimidazolyl; or $-(CH_2)_nCOOR^8$ where n=0-4 and R^8 is selected from hydrogen; straight or branched (C_1-C_3)alkyl selected from methyl, ethyl, n-propyl or 1-methylethyl; or (C_6-C_{10})aryl selected from phenyl, α-naphthyl or β-naphthyl; with the proviso that R^6 and R^7 cannot both be hydrogen;
or R^6 and R^7 taken together are $-(CH_2)_2B(CH_2)_2-$, wherein B is selected from $(CH_2)_n$ and n=0-1, -NH, $-N(C_1$-$C_3)$alkyl [straight or branched], $-N(C_1$-$C_4)$alkoxy, oxygen, sulfur or substituted congeners selected from (L or D)proline, ethyl(L or D)prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts or metal complexes.

Compounds of special interest are compound according to formula I and II wherein:
R is a halogen selected from bromine, chlorine and iodine; or $R = -NR^1R^2$
and when $R = -NR^1R^2$ and R^1 = methyl or ethyl.

R^2 = methyl or ethyl.
R^3 is selected from hydrogen;
R^4 is selected from hydrogen and $(C_1$-$C_2)$alkyl selected from methyl and ethyl.
when R^3 does not equal R^4 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the substituent W) may be either the racemate (DL) or the individual enantiomers (L or D);
W is selected from $(C_7$-$C_{12})$ straight or branched alkyl monosubstituted amino group substitution selected from heptyl, octyl, nonyl, decyl, undecyl, dodecyl and the diastereomers and enantiomers of said branched alkyl monosubstituted amino group; (C_2)fluoroalkylamino group selected from 2,2,2-trifluoroethyl and 3,3,3-trifluoropropyl; [$(C_4$-$C_5)$cycloalkyl]alkyl monosubstituted amino group substitution selected from (cyclopropyl)-methyl and (cyclopropyl) ethyl; $(C_3$-$C_4)$alkenyl and alkynyl monosubstituted amino group substitution selected from allyl and propynyl; $(C_2$-$C_7)$ azacycloalkyl and substituted $(C_2$-$C_7)$azacycloalkyl group substitution selected from 4-methylpiperidinyl, 4-hydroxypiperidinyl and 4-(hydroxymethyl)piperidinyl; substituted 1-azaoxacycloalkyl group substitution selected from 2-$(C_1$-$C_3)$ alkylmorpholinyl; [1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group selected from piperazinyl and 4-$(C_1$-$C_3)$alkylpiperazinyl;
1-azathiacycloalkyl and substituted 1-azathiacycloalkyl group selected from thiomorpholinyl and 2-$(C_1$-$C_3)$alkylthiomorpholinyl; (heterocycle)methylamino group selected from 2- or 3-thienylmethylamino and 2-, 3- or 4-pyridylmethylamino;
1,1-disubstituted hydrazino group selected from 1,1-dimethylhydrazino and N-amino-piperidinyl. [β or γ-$(C_1$-$C_3)$acylamido]alkylamino group substitution selected from 2-(acetamido)ethyl; β or γ-$(C_1$-$C_3)$alkoxyalkylamino group substitution selected from 2-methoxyethyl, 2-ethoxyethyl, 2,2-diethoxyethyl, 2-methoxypropyl and 3-methoxypropyl;
β, γ or δ $(C_2$-$C_4)$hydroxyalkylamino selected from 4-hydroxybutyl and 3-hydroxypropyl; or R^3 and W taken together are selected from $-(CH_2)_n(R^5)N-$, n= 3, and R^5 is selected from hydrogen and trifluoroacetyl;
R^6 is selected from hydrogen; straight or branched $(C_1$--$C_3)$alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl;
R^7 is selected from hydrogen; straight or branched $(C_1$-$C_3)$alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; with the proviso that R^6 and R^7 cannot both be hydrogen;
or R^6 and R^7 taken together are $-(CH_2)_2B(CH_2)_2-$, wherein B is selected from (CH_2)n and n=0-1, -NH, $-N(C_1$-$C_3)$alkyl [straight or branched], $-N(C_1$-$C_4)$alkoxy, oxygen, sulfur or substituted congeners selected from (L or D)proline, ethyl (L or D)prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts or metal complexes.

Intermediates for producing the above compounds of formula I and II, include those having the formula III:



III

wherein:
Y is selected from bromine, chlorine, fluorine or iodine;
R is a halogen selected from bromine, chlorine,
fluorine and iodine; or R = $-NR^1R^2$ and when R = $-NR^1R^2$ and R^1 = hydrogen,
R^2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl; and when R^1 = methyl or ethyl.
R^2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;
and when R^1 = n-propyl,
R^2 = n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;
and when R^1 = 1-methylethyl,
R^2 = n-butyl, 1-methylpropyl or 2-methylpropyl;
and when R^1 = n-butyl,
R^2 = n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R^1 = 1-methylpropyl,
R^2 = 2-methylpropyl;
R^3 is selected from hydrogen, straight or branched (C_4--C_8)alkyl group selected from butyl, isobutyl, pentyl, hexyl, heptyl and octyl;
α-mercapto(C_1-C_4)alkyl group selected from mercaptomethyl, α-mercaptoethyl, α-mercapto-1-methylethyl and α-mercaptopropyl; α-hydroxy-(C_1-C_4)alkyl group selected from hydroxymethyl, α-hydroxyethyl, α-hydroxy-1-methylethyl and α-hydroxypropyl; carboxyl(C_1-C_8)alkyl group; (C_6-C_{10})aryl group selected from phenyl, α-naphthyl and β-naphthyl; substituted(C_6-C_{10})aryl group (substitution selected from hydroxy, halogen, (C_1-C_4)alkoxy, trihalo(C_1-C_3)alkyl, nitro, amino, cyano, (C_1-C_4)alkoxycarbonyl, (C_1-C_3)alkylamino and carboxy); (C_7-C_9)aralkyl group selected from benzyl, 1-phenylethyl 2-phenylethyl and phenylpropyl; substituted (C_7--C_9)aralkyl group [substitution selected from halo, (C_1--C_4)alkyl, nitro, hydroxy, amino, mono-or di-substituted (C_1--C_4)alkylamino, (C_1-C_4)alkoxy, (C_1-C_4)alkylsulfonyl, cyano and carboxy];
R^4 is selected from hydrogen and (C_1-C_6)alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl;
when R^3 does not equal R^4 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the substituent W) maybe be either the racemate (DL) or the individual enantiomers (L or D); and the pharmacologically acceptable organic and inorganic salts or metal complexes;

Preferred compounds are compounds according to the above formula III wherein:
Y is selected from bromine, chlorine, fluorine or iodine;
R is a halogen selected from bromine, chlorine, fluorine and iodine; or R = -NR^1R^2 and when R = -NR^1R^2 and R^1 = hydrogen,
R^2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, or 2-methylpropyl;
R^3 is selected from hydrogen; straight or branched (C_4--C_8)alkyl group selected from butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α-hydroxy(C_1-C_4)alkyl group selected from hydroxymethyl, α-hydroxyethyl, α-hydroxy-1-methylethyl and α-hydroxypropyl; carboxyl(C_1-C_8)alkyl group; (C_6-C_{10})aryl group selected from phenyl, α-naphthyl and β-naphthyl; substituted(C_6-C_{10})aryl group (substitution selected from hydroxy, halogen, (C_1-C_4)alkoxy, (C_1-C_4)alkoxy-carbonyl and carboxy); (C_7-C_9)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenyl-propyl; substituted (C_7-C_9)aralkyl group [substitution selected from halo, (C_1--C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)alkylsulfonyl, cyano and carboxy];
R^4 is selected from hydrogen and (C_1-C_4)alkyl selected from methyl, ethyl, propyl, isopropyl, butyl and isobutyl;
when R^3 does not equal R^4 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the substituent W) maybe be either the racemate (DL) or the individual enantiomers (L or D); and the pharmacologically acceptable organic and inorganic salts or metal complexes.

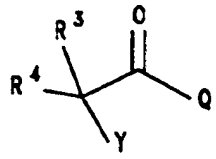
Particularly preferred compounds are compounds according to formula III wherein:
Y is selected from bromine, chlorine, fluorine or iodine;
R is a halogen selected from bromine, chlorine, fluorine and iodine; or R = -NR^1R^2 and when R = -NR^1R^2 and R^1 = hydrogen,
R^2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl;
and when R^1 = methyl or ethyl,
R^2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;
R^3 is selected from hydrogen; straight or branched (C_4--C_6)alkyl group selected from butyl, isobutyl, pentyl and hexyl; (C_6-C_{10})aryl group selected from phenyl, α-naphthyl and β-naphthyl; (C_7-C_9)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl;
R^4 is selected from hydrogen and (C_1-C_3)alkyl selected from methyl, ethyl, propyl and isopropyl;
when R^3 does not equal R^4 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the substituent W) maybe be either the racemate (DL) or the individual enantiomers (L or D); and the pharmacologically acceptable organic and inorganic salts or metal complexes.

Compounds of special interest are compound according to formula III wherein:
Y is selected from bromine, chlorine, fluorine or iodine;
R is a halogen selected from bromine, chlorine and iodine; or R = -NR^1R^2
and when R = -NR^1R^2 and R^1 = methyl or ethyl,
R^2 = methyl or ethyl,
R^3 is selected from hydrogen;
R^4 is selected from hydrogen and (C_1-C_2)alkyl selected from methyl and ethyl;
when R^3 does not equal R^4 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the substituent W) maybe be either the racemate (DL) or the individual enantiomers (L or D); and the pharmacologically acceptable organic and inorganic salts or metal complexes.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

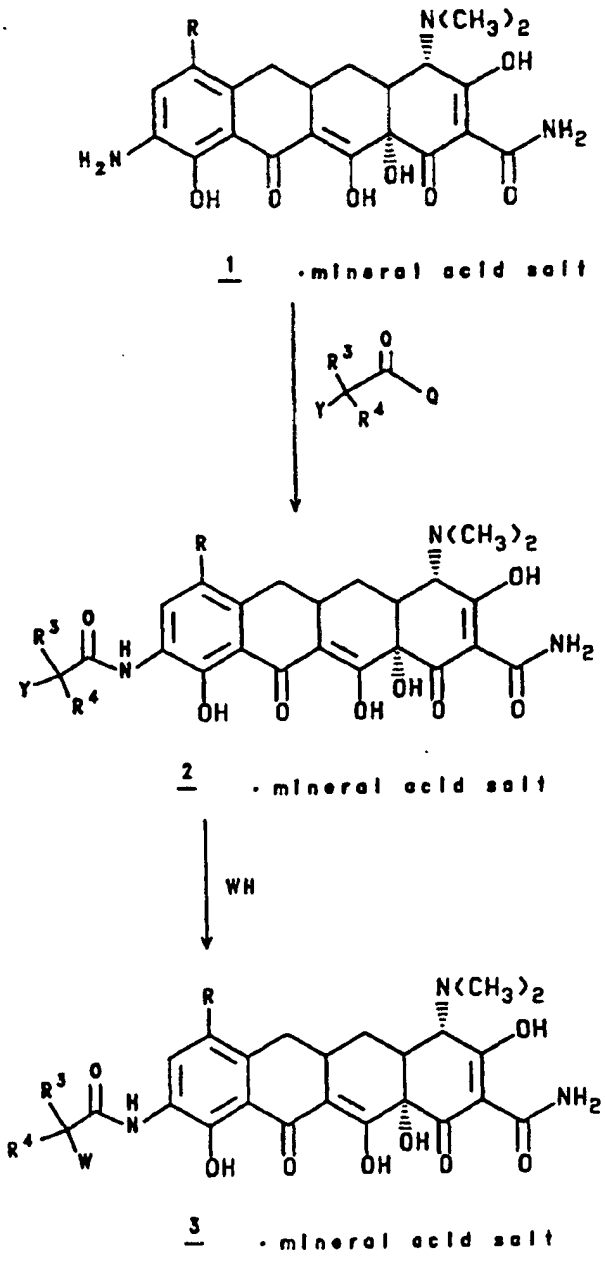
The novel compounds of the present invention may be readily prepared in accordance with the following schemes

The preferred method for producing 7-(substituted)-9-[(substituted glycyl)amido]-6-demethyl-6-deoxytetracyclines or the mineral acid salts, 3, is shown in scheme I. This method uses common intermediates which are easily prepared by reacting commercially available haloacyl halides of the formula:



wherein Y, R^3 and R^4 are as defined hereinabove and Q is halogen selected from bromine, chlorine, iodine and fluorine; with 9-amino-7-(substituted)-6-demethyl-6-deoxytetracycline or its mineral acid salt, 1, to give straight or branched 9-[(haloacyl)amido]-7-(substituted)-6-demethyl-6-deoxytetracyclines or mineral acid salts 2, in almost quantitative yield. The above intermediates, straight or branched 9-[(haloacyl)-amido]-7-(substituted)-6-demethyl-6-deoxytetracyclines or mineral acid salts, 2, react with a wide variety of nucleophiles, especially amines, having the formula WH, wherein W is as defined hereinabove, to give a new 7-(substituted)-9-[(substituted glycyl)amido]-7-(substituted)-6-demethyl-6-deoxytetracyclines or the mineral acid salts, 3 of the present invention.

Scheme I

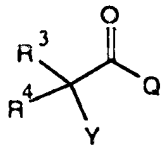


In accordance with scheme I. 9-amino-7-(sub-stituted)-6-demethyl-6-deoxytetracycline or its mineral acid salt, 1 is mixed with

a) a polar-aprotic solvent such as 1,3-dimethyl-3 4,5,6-tetrahydro-2(1H)pyrimidone, herein after called DMPU, hexamothylphosphoramido herein after called HMPA, dimothylformamido. dimothylacetamido, N-methylpyrrolidone, 1,2-dimethoxyethane or equivalent thereof;

b) an inert solvent such as acetonitrile, methylene chloride, tetrahydrofuran chloroform. carbon tetrachloride

1,2-dichloroethane, tetrachloroethane, diethyl ether, t-butyl methyl ether, isopropyl ether or equivalent thereof;
c) a base such as sodium carbonate, sodium bicarbonate, sodium acetate, potassium carbonate, potassium bicarbonate, triethylamine, cesium carbonate, lithium carbonate or bicarbonate equivalents; and
d) a straight or branched haloacyl halide of the formula:



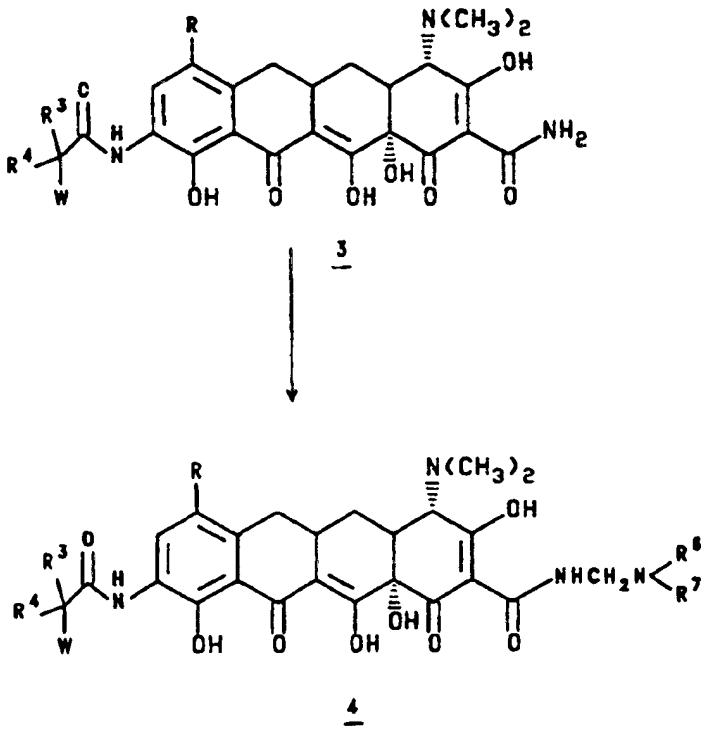
wherein Y, R^3, R^4 and Q are as hereinabove defined, such as bromoacetyl bromide, chloroacetyl chloride, 2-bromopropionyl bromide or equivalent thereof; the halo, Y, and halide, Q, in the haloacyl halide can be the same or different halogen and is selected from bromine, chlorine, iodine and fluorine; Y is halogen;
e) for 0.5 to 5 hours at from room temperature to the reflux temperature of the reaction.

to form the corresponding 9-[(haloacyl)amido-7-(substituted)-6-demethyl-6-deoxytetracycline, 2 , or its mineral acid salt.

The intermediate, 9-[(haloacyl)amido]-7-(substituted)-6-demethyl-6-deoxytetracycline or its mineral acid salt, 2, is treated, under an inert atmosphere of helium, argon or nitrogen, with

a) a nucleophile WH such as an amine, substituted amine or equivalent thereof for example methylamine, dimethylamine, ethylamine, n-butylamine, propylamine or n-hexylamine;
b) a polar-aprotic solvent such as DMPU, HMPA dimethylformamide, dimethylacetamide, N-methylpyrrolidone or 1,2-dimethoxyethane;
c) for from 0.5 - 2 hours at room temperature or under reflux temperature to produce the desired 7-(substituted)-9-[(substituted glycyl)amido]-6-demethyl-6-deoxytetracycline, 3, or its mineral acid salt.

Scheme II



In accordance with Scheme II, compounds of formula 3 are N-alkylated in the presence of formaldehyde and either a primary amine such as methylamine, ethylamine, benzylamine, methyl glycinate. (L or D)alanine, (L or D)lysine or their substituted congeners; or a secondary amine such as morpholine, pyrrolidine, piperidine or their substituted congeners to give the corresponding Mannich base adduct, 4.

The 7-(substituted)-9-[(substituted glycyl)amido]-6-demethyl-6-deoxytetracyclines may be obtained as metal complexes such as aluminum, calcium, iron, magnesium, manganese and complex salts; inorganic and organic salts and corresponding Mannich base adducts using methods known to those skilled in the art (Richard C. Larock, Comprehensive Organic Transformations, VCH Publishers, 411-415, 1989). It is well known to one skilled in the art that an appropriate salt form is chosen based on physical and chemical stability, flowability, hygroscopicity and solubility. Preferably, the 7-(substituted)-9-[(substituted glycyl)amido]-6-demethyl-6-deoxytetracyclines are obtained as inorganic salt such as hydrochloric, hydrobromic, hydroiodic. phosphoric, nitric or sulfate; or organic salt such as acetate, benzoate. citrate, cysteine or other amino acids, fumarate, glycolate, maleate, succinate tartrate, alkylsulfonate or arylsulfonate. Depending on the stochiometry of the acids used, the salt formation occurs with the C(4)-dimethylamino group (1 equivalent of acid) or with both the C(4)-dimethylamino group and the W group (2 equivalents of acid). The salts are preferred for oral and parenteral administration.

Some of the compounds of the hereinbefore described Schemes have centers of asymmetry at the carbon bearing the W substituent. The compounds may, therefore, exist in at least two (2) stereoisomeric forms. The present invention encompasses the racemic mixture of stereoisomers as well as all stereoisomers of the compounds whether free from other stereoisomers or admixed with stereoisomers in any proportion of enantiomers. The absolute configuration of any compound may be determined by conventional X-ray crystallography.

The stereochemistry centers on the tetracycline unit (i.e. C-4, C-4a, C-5a and C-12a) remain intact throughout the reaction sequences.

BIOLOGICAL ACTIVITY

Methods for in Vitro antibacterial evaluation (Table I)

The minimum inhibitory concentration (MIC), the lowest concentration of the antibiotic which inhibits growth of the test organism, is determined by the agar dilution method using 0.1 ml Muller-Hinton II agar (Baltimore Biological Laboratories) per well. An inoculum density of 1-5 x 10^5 CFU/ml, and an antibiotic concentrations range of 32-0.004 microgram/ml is used. MIC is determined after the plates are incubated for 18 hours at 35°C in a forced air incubator. The test organisms comprise strains that are sensitive to tetracycline and genetically defined strains that are resistant to tetracycline, due to inability to bind bacterial ribosomes (tetM).

E. coli in Vitro Protein Translation System (Table II)

An in vitro, cell free, protein translation system using extracts from E. coli strain MRE600 (tetracycline sensitive) and a derivative of MRE600 containing the tetM determinant has been developed based on literature methods [J.M. Pratt, Coupled Transcription-translation in Prokaryotic Cell-free Systems, Transcription and Translation, a Practical Approach. (B.D. Hames and S.J. Higgins, eds) p. 179-209, IRL Press, Oxford-Washington, 1984].

Using the system described above, the tetracycline compounds of the present invention are tested for their ability to inhibit protein synthesis in vitro. Briefly, each 10 microliter reaction contains S30 extract (a whole extract) made from either tetracycline sensitive cells or an isogenic tetracycline resistant (tetM) strain, low molecular weight components necessary for transcription and translation (i.e. ATP and GTP), a mix of 19 amino acids (no methionine), ^{35}S labeled methionine, DNA template (either pBR322 or pUC119), and either DMSO (control) or the novel tetracycline compound to be tested ("novel TC") dissolved in DMSO.

The reactions are incubated for 30 minutes at 37 C. Timing is initiated with the addition of the S30 extract, the last component to be added. After 30 minutes, 2.5 µl of the reaction is removed and mixed with 0.5 ml of 1N NaOH to destroy RNA and tRNA. Two ml of 25% trichloroacetic acid is added and the mixture incubated at room temperature for 15 minutes. The trichloroacetic acid precipitated material is collected on Whatman GF/C filters and washed with a solution of 10% trichloroacetic acid. The filters are dried and the retained radioactivity, representing incorporation of ^{35}S-methionine into polypeptides, is counted using standard liquid scintillation methods.

The percent inhibition (P.I.) of protein synthesis is determined to be:

$$P.I. = 100 - \left(\frac{\text{Retained radioactivity of novel TC containing sample}}{\text{Retained radioactivity of the DMSO control reaction}} \right) \times 100$$

In Vivo Antibacterial Evaluation

The therapeutic effects of tetracyclines are determined against an acute lethal infection with Staphylococcus aureus strain Smith (tetracycline sensitive). Female, mice, strain CD-1(Charles River Laboratories), 20±2 grams, are challenged by an intraperitoneal injection of sufficient bacteria (suspended in hog mucin) to kill non-treated controls within 24-48 hours. Antibacterial agents, contained in 0.5 ml of 0.2% aqueous agar, are administered subcutaneously or orally 30 minutes after infection. When an oral dosing schedule is used, animals are deprived of food for 5 hours before and 2 hours after infection. Five mice are treated at each dose level. The 7 day survival ratios from 3 separate tests are pooled for calculation of median effective dose (ED_{50}).

Testing Results

The claimed compounds exhibit antibacterial activity against a spectrum of tetracycline sensitive and resistant Gram-positive and Gram-negative bacteria, especially, strains of E. coli, S. aureus and E faecalis, containing tetM and tetD resistance determinants; and E. coli containing the tetB and tetD resistance determinants. Notable are compounds D, G, and K, as shown in Table I which demonstrated excellent in vitro activity against tetracycline resistant strains containing the tetM resistance determinant (such as S. aureus UBMS 88-5, S. aureus UBMDS 90-1 and 90-2, E. coli UBMS 89-1 and 90-4) and tetracycline resistant strains containing tetB resistance determinants (such as E. coli UBMS 88-1 and E. coli TN10C tetB). These compounds also have good activity against E. coli tetA, E. coli tetC and E. coli tetD and are equally as effective as minocycline against susceptible strains and are superior to that of minocycline against a number of recently isolated bacteria from clinical sources (Table I).

Minocycline and compounds B, C, D, G and H are assayed in vitro for their ability to inhibit protein synthesis taking

place on either wild type or tetM protected ribosomes using a coupled transcription and translation system. All compounds are found to effectively inhibit protein synthesis occuring on wild type ribosomes, having equivalent levels of activity. Minocycline is unable to inhibit protein synthesis occurring on tetM protected ribosomes. In contrast, compounds B, C, D, G and H are effective at inhibiting protein synthesis occurring on tetM protected ribosomes (Table II).

Compounds B, C, D, G and H bind reversibly to its target (the ribosome) since bacterial growth resumes when the compound is removed from the cultures by washing of the organism. Therefore, the ability of these compounds to inhibit bacterial growth appears to be a direct consequence of its ability to inhibit protein synthesis at the ribosome level.

The activity of compound G against tetracycline susceptible organisms is also demonstrated in vivo in animals infected with S. aureus Smith with ED_{50}'s between 1-2 mg/kg when administered intravenously, and ED_{50}'s of 4-8 mg/kg when given orally.

The improved efficacy of compounds D, G and K is demonstrated by the in vitro activity against isogenic strains into which the resistance determinants, such as tetM and tetB, were cloned (Table I), and the inhibition of protein synthesis by tetM ribosomes (Table II).

As can be seen from Table I and II, compounds of the invention may also be used to prevent or control important veterinary diseases such as diarrhea, urinary tract infections, infections of skin and skin structure, ear nose and throat infections, wound infections, mastitis and the like.

COMPOUND LEGEND FOR TABLES

A [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a, 12-octahydro-1,8,10a, 11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1-(trifluoroacetyl)-2-pyrrolidinecarboxamide dihydrochloride

B [4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10, 12,12a-tetrahydroxy-9-[[[(2-(methoxyethyl)-amino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride

C [4S-(4alpha,12aalpha)]-9-[[[(2,2-Diethoxyethyl)amino]acetyl]amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a, 6,11,12a-octahydro-3,10, 12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride

D [4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10, 12,12a-tetrahydroxy-1,11-dioxo-9-[[(2-propenylamino)acetyl]amino]-2-naphthacenecarboxamide dihydrochloride

E [4S-(4alpha,12aalpha)]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10, 12,12a-tetrahydroxy-1,11-dioxo-9-[[[(2-pyridinylmethyl)amino]acetyl]amino-2-naphthacenecarboxamide dihydrochloride

F [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a, 11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-thiomorpholineacetamide dihydrochloride

G [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a, 11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-methyl-1-piperidineacetamide dihydrochloride

H [4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10, 12,12a-tetrahydroxy-9-[[[(3-methoxypropyl)-amino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride

I [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a, 11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-methyl-1-piperazineacetamide dihydrochloride

J [4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-9-[[(heptylamino)acetyl]amino]-1,4,4a, 5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride

K [4S-(4alpha,12aalpha)]-9-[[(Cyclopropylmethyl)amino]acetyl]amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10, 12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride

L [4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10, 12,12a-tetrahydroxy-1,11-dioxo-9-[[(undecylamino)acetyl]amino]-2-naphthacenecarboxamide dihydrochloride

M [4S-(4alpha,12aalpha)]-9-[(Bromoacetyl)-amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6, 11,12a-octahydro-3,10, 12,12a-tetrahydroxy-1, 11-dioxo-2-naphthacenecarboxamide dihydrochloride

N Tetracycline

O Minocycline

P [4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-12,12a-tetrahydroxy-9-[[[(2-hydroxyethyl)-amino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride

Q [4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-12,12a-tetrahydroxy-9-[[[(2-hydroxyethyl)-methylamino]acetyl]amino-1,11-dioxo-2-naphthacenecarboxamide

R [4S-(4alpha,12aalpha)]-4,7-Bis(dimethyl-4-amino-1-amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[(4-(hydroxybutyl)amino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide

S [4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-12,12a-tetrahydroxy-1,11-dioxo-9-[[[2,2,2-trifluoroethyl)amino]acetyl]amino-2-naphthacenecarboxamide

U [4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[[2-(1-piperidinyl)ethyl]amino]acetyl]-amino]-2-naphthacenecarboxamide

V [4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-12,12a-tetrahydroxy-9-[[[me-

thyl-2-propynylamino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide

W [4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,-12,12a-tetrahydroxy-hydroxy-1,11-dioxo-9-[[(1-piperidinylamino)acetyl]amino]-2-naphthacenecarboxamide

X [4S-(4-alpha 12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a 5,5a 6,11,12a-octahydro-3,10,-12,12a-tetrahydroxy-1,11-dioxo-9-[[[(phenylmethoxy)amino]acetyl]amino)-2-naphthacenecarboxamide

Table I

ANTIBACTERIAL ACTIVITY OF 9-((SUBSTITUTED GLYCYL)AMIDO)-6-DEMETHYL-6-DEOXYTETRACYCLINES

MIC (µg/ml)

Organism	Compound A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
E. coli UBMS 88-1 Tet B	8	2	16	1	16	>32	2	2	8	2	0.5	32	>32	>32	16
E. coli J3272 Tet sens.	8	2	8	0.5	NT	>32	1	1	NT	NT	NT	NT	16	0.5	0.5
E. coli MC 4100 Tet sens.	NT	NT	NT	NT	2	NT	NT	NT	1	1	0.12	2	NT	NT	NT
E. coli PRP1 Tet A	>32	8	>32	8	32	>32	2	4	16	2	4	32	>32	32	4
E. coli MC 4100 TNIOC Tet B	8	2	8	1	NT	>32	2	2	NT	NT	NT	NT	>32	>32	8
E. coli J3272 Tet C	8	4	16	1	16	>32	1	1	8	2	0.5	32	>32	>32	2
E. coli UBMS 89-1 Tet M	8	2	4	0.5	8	>32	0.5	2	8	0.5	0.5	16	4	8	8
E. coli UBMS 89-2 Tet sens.	8	2	8	0.5	16	>32	2	1	8	2	0.5	16	32	1	0.5
E. coli J2175	8	2	8	0.5	16	>32	1	1	8	2	0.5	16	32	1	0.5
E. coli BAJ9003 IMP MUT	1	0.25	0.5	0.12	1	0.5	0.12	0.12	0.5	0.25	0.12	1	0.25	0.25	0.03
E. coli UBMS 90-4 Tet M	NT	2	4	0.5	8	>32	1	1	8	2	0.5	32	NT	16	>32
E. coli UBMS 90-5	4	2	8	0.5	16	>32	2	1	8	2	0.5	16	16	1	0.5
E. coli #311 (MP)	8	2	8	0.5	8	>32	1	1	8	2	0.5	8	8	1	0.25
E. coli ATCC 25922	8	2	8	0.5	8	32	1	1	8	2	0.5	8	16	0.5	0.5
E. coli J3272 Tet D	2	1	4	0.25	8	16	0.25	0.5	4	2	0.25	32	32	>32	8
S. mariescens FPOR 8733	>32	>32	>32	8	>32	>32	16	16	>32	16	8	>32	>32	32	2
X. maltophilia NEMC 87210															
Ps. acruginosa ATCC 27853	>32	>32	>32	16	>32	>32	32	32	>32	>32	16	>32	>32	8	8
S. aureus NEMC 8769	1	0.5	0.25	0.12	8	0.25	0.12	0.25	0.5	no growth	1	0.5	0.12	0.03	≤0.015

Table 1 (cont'd)

ANTIBACTERIAL ACTIVITY OF 9-[(SUBSTITUTED GLYCYL)AMIDO]-6-DEMETHYL-6-DEOXYTETRACYCLINES

MIC (μg/ml)

Organism	Compound														
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
S. aureus UBMS 88-4	4	0.5	1	0.25	8	1	0.5	1	2	0.5	0.5	0.5	0.5	0.06	0.03
S. aureus UBMS 88-5 Tet M	4	1	1	0.25	8	1	0.5	0.5	4	0.5	1	16	1	>32	4
S. aureus UBMS 88-7 Tet K	16	16	8	8	32	4	0.5	8	16	1	4	2	2	>32	0.12
S. aureus UBMS 90-1 Tet M	8	2	1	0.5	8	1	0.5	2	8	1	1	16	1	32	4
S. aureus UBMS 90-3	1	0.5	0.5	0.25	4	1	0.5	0.5	2	0.5	0.5	0.5	0.5	0.06	0.03
S. aureus UBMS 90-2 Tet M	2	0.5	1	0.25	8	1	0.5	0.5	2	0.5	0.5	4	0.5	32	2
S. aureus IVES 2943	16	32	8	8	>32	4	0.5	16	>32	0.5	8	16	4	>32	2
S. aureus ROSE (MP)	32	32	16	8	>32	8	1	16	>32	2	8	16	8	>32	0.5
S. aureus SMITH (MP)	2	0.5	0.5	0.12	4	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.06	0.03
S. aureus IVES 1 983	16	32	16	8	>32	4	0.5	16	>32	1	8	16	4	>32	2
S. aureus ATCC 29213	4	1	1	0.25	8	1	0.5	1	2	0.5	1	1	0.5	0.06	0.03
S. hemolyticus AVHAH 88-3	8	2	2	0.5	16	4	1	2	16	2	2	8	2	0.5	0.12
Enterococcus 12201	0.5	0.5	1	0.25	4	1	0.25	0.5	2	0.5	0.25	4	1	32	8
E. faecalis ATCC 29212	2	0.25	0.5	0.12	2	0.25	0.12	0.25	1	0.25	0.25	2	0.5	8	1

Table 1 (cont'd)

ANTIBACTERIAL ACTIVITY OF 9-[(SUBSTITUTED GLYCYL)AMIDO]-6-DEMETHYL-6-DEOXYTETRACYCLINES

MIC (μg/ml)

Organism	Compound P	Q	R	S	U	V	W	X
E. coli UBMS 88-1 Tet B	>32	32	>32	32	>32	>32	>32	>32
E. coli J3272 Tet sens.	NT	NT	NT	NT	NT	NT	NT	NT
E. coli MC 4100 Tet sens.	4	4	8	16	4	32	32	4
E. coli PRP1 Tet A	>32	>32	>32	>32	>32	>32	>32	>32
E. coli MC 4100 TN10C Tet B	>32	>32	>32	>32	32	>32	>32	>32
E. coli J3272 Tet C	>32	>32	>32	>32	16	>32	>32	>32
E. coli UBMS 89-1 Tet M	>32	32	32	32	16	>32	>32	16
E. coli UBMS 89-2 Tet sens.	>32	32	32	>32	32	>32	>32	>32
E. coli J2175	32	32	32	>32	32	>32	>32	>32
E. coli BAJ9003 IMP MUT	2	2	4	1	2	4	16	1
E. coli UBMS 90-4 Tet M	32	16	32	>32	16	>32	>32	>32
E. coli UBMS 90-5	32	32	32	>32	16	>32	>32	>32
E. coli #311 (MP)	16	32	32	>32	16	>32	>32	16
E. coli ATCC 25922	16	32	32	>32	16	>32	>32	16
E. coli J3272 Tet D	16	32	8	>32	8	>32	>32	16
S. mariescens FPOR 8733	>32	16	8	>32	>32	>32	>32	>32
X. maltophilia NEMC 87210	>32	8	8	16	16	32	>32	16
Ps. aeruginosa ATCC 27853	>32	>32	>32	>32	>32	>32	>32	>32
S. aureus NEMC 8769	4	8	8	4	8	4	>32	1

Table 1 (cont'd)

ANTIBACTERIAL ACTIVITY OF 9-[(SUBSTITUTED GLYCYL)AMIDO]-6-DEMETHYL-6-DEOXYTETRACYCLINES

MIC (μg/ml)

Organism	Compound P	Q	R	S	U	V	W	X
S. aureus UBMS 88-4	8	8	8	4	8	4	>32	1
S. aureus UBMS 88-5 Tet M	32	16	32	8	16	8	>32	2
S. aureus UBMS 88-7 Tet K	32	32	32	32	16	32	>32	4
S. aureus UBMS 90-1 Tet M	32	32	32	16	32	16	>32	2
S. aureus UBMS 90-3	8	8	8	4	8	4	16	1
S. aureus UBMS 90-2 Tet M	16	16	16	4	8	8	>32	2
S. aureus IVES 2943	>32	>32	>32	>32	>32	>32	>32	8
S. aureus ROSE (MP)	>32	>32	>32	>32	>32	>32	>32	16
S. aureus SMITH (MP)	4	8	8	1	8	4	16	0.5
S. aureus IVES 1 983	>32	>32	>32	>32	>32	>32	>32	8
S. aureus ATCC 29213	8	16	16	4	8	4	32	1
S. hemolyticus AVNAH 88-3	32	16	32	16	32	32	>32	4
Enterococcus 12201	8	4	8	4	8	8	>32	4
E. faecalis ATCC 29212	4	4	8	2	8	4	>32	1

NT = Not tested

Table II

In Vitro Transcription and Translation Sensitivity to Tetracycline Compounds			
		% Inhibition	
Compound	Conc	Wild Type S30	TetM S30
B	1.0 mg/ml	98	97
	0.25 mg/ml	96	95
	0.06 mg/ml	92	91
C	1.0 mg/ml	98	96
	0.25 mg/ml	95	84
	0.06 mg/ml	88	65
D	1.0 mg/ml	99	98
	0.25 mg/ml	98	96
	0.06 mg/ml	93	83
G	1.0 mg/ml	99	99
	0.25 mg/ml	97	92
	0.06 mg/ml	90	83
H	1.0 mg/ml	99	98
	0.25 mg/ml	96	94
	0.06 mg/ml	88	85
O	1.0 mg/ml	98	68
	0.25 mg/ml	89	43
	0.06 mg/ml	78	0

When the compounds are employed as antibacterials, they can be combined with one or more pharmaceutically acceptable carriers, for example, solvents, diluents and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing, for example, from about 0.05 to 5% of suspending agent, syrups containing, for example, from about 10 to 50% of sugar, and elixirs containing for example, from about 20 to 50% ethanol and the like, or parenterally in the form of sterile injectable solutions or suspensions containing from about 0.05 to 5% suspending agent in an isotonic medium. Such pharmaceutical preparations may contain, for example, from about 25 to about 90% of the active ingredient in combination with the carrier, more usually between about 5% and 60% by weight.

An effective amount of compound from 2.0 mg/kg of body weight to 100.0 mg/kg of body weight should be administered one to five times per day via any typical route of administration including but not limited to oral, parenteral (including subcutaneous, intravenous, intramuscular, intrasternal injection or infusion techniques), topical or rectal, in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

These active compounds may be administered orally as well as by intravenous, intramuscular or subcutaneous routes. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid

compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the compounds is preferred.

These active compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in glycerol, liquid, polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserve against the contaminating action of microorganisms such as bacterial and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oil.

The invention will be more fully described in conjunction with the following specific examples which are not be construed as limiting the scope of the invention.

Example 1

[4S-(4alpha,12aalpha)]-9-[(Chloroacetyl)amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,-10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride

To a room temperature solution of 0.334 g of 9-amino-4,7-bis(dimethyamino)-6-demethyl-6-deoxytetracycline disulfate, 6 ml of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone, hereinafter called DMPU, and 2 ml of acetonitrile is added 0.318 g of sodium carbonate. The mixture is stirred for 5 minutes followed by the addition of 0.068 g of chloroacetyl chloride. The reaction is stirred for 30 minutes, filtered, and the filtrate added dropwise to 100 ml of diethyl ether, containing 1 ml of 1M hydrochloric acid in diethyl ether. The resulting solid is collected and dried to give 0.340 g of the desired intermediate. MS(FAB): m/z 549 (M+H).

Example 2

[4S-(4alpha,12aalpha)]-9-[(Bromoacetyl)amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,-10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide monohydrobromide

The title compound is prepared by the procedure of Example 1, using 6.68 g of 9-amino-4,7-bis(dimethylamino)-6-demethyl-6-deoxytetracycline disulfate, 50 ml of DMPU, 30 ml of acetonitrile, 6.68 g of sodium carbonate and 0.215 g of bromoacetyl bromide. 5.72 g of the desired intermediate is obtained.
MS(FAB): m/z 593 (M+H).

Example 3

[4S-(4alpha,12aalpha)]-9-[(2-Bromo-1-oxopropyl)amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide sulfate

The title compound is prepared by the procedure of Example 1, using 1.00 g of 9-amino-4,7-bis(dimethylamino)-6-demethyl-6-deoxytetracycline disulfate, 1.0 g of sodium carbonate and 0.648 g of 2-bromopropionyl bromide to give 0.981 g of the desired product.
MS(FAB): m/z 607 (M+H).

Example 4 [4S-(4alpha,12aalpha)]-9-[(4-Bromo-1-oxobutyl)amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride

The title compound is prepared by the procedure of Example 1, using 1.34 g of 9-amino-4,7-bis(dimethylamino)-6-demethyl-6-deoxytetracycline disulfate, 1.3 of sodium carbonate, 24 ml of DMPU, 8 ml of acetonitrile and 0.389 g of 4-bromobutyryl chloride to give 1.45 g of the desired product.

Example 5 [7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-1-trifluoroacetyl)-2-pyrrolidinecarboxamide dihydrochloride

The title compound is prepared by the procedure of Example 1, using 0.334 g of 9-amino-4,7-bis(dimethylamino)-

6-demethyl-6-deoxytetracycline disulfate, 10 ml of DMPU, 2 ml of acetonitrile, 0.34 g of sodium carbonate and 7.5 ml of 0.1M (S)-(-)-N-(trifluoroacetyl)prolyl chloride to give 0.292 g of the desired product.
MS(FAB): m/z 666 (M+H).

Example 6

[4S-(4alpha,12aalpha)]-9-[[[(Cyclopropylmethyl)amino]acetyl]amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide 2-naphthacenecarboxamide dihydrochloride

A mixture of 0.20 g of product from Example 2, 0.50 g of (aminomethyl)cyclopropane and 5 ml of DMPU, under Argon, is stirred at room temperature for 1 hour. The excess amine is removed in vacuo and the residue diluted with a small volume of methyl alcohol. The diluted reaction solution is added dropwise to a misture of diethyl ether and 5 ml of 2-propanol. 1M Hydrochloric acid in diethyl ether is added until a solid is formed. The resulting solid is collected and dried to give 0.175 g of the desired product.
MS(FAB): m/z 584 (M+H)

Substantially following the methods described in detail herein above in Example 6, the compounds of this invention listed below in Examples 7 - 16 are prepared.

Example #	Name	Starting Material Prod. of Exp.	Reactant	Rx Time	MS(FAB): m/z
7	[4S-(4alpha,12aalpha)]-9-[[[(2,2-Diethoxyethyl)amino]acetyl]amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,-12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride	2or1	2,2-Diethoxy-ethylamine	3 hrs.	646(M+H)
8	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethyl-amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[2-(methoxy-ethyl)amino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride	2or1	2-Methoxy-ethylamine	2 hr.	588(M+H)
9	[4S-(4alpha,12aalpha)]-4,7-Bis(di-methylamino)-1,4,4a,5,5a,6,11,12a-octa-hydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(2-propenylamino)acetyl]amino]-2-naphthacenecarboxamide dihydrochloride	2or1	Allylamine	2 hr.	570(M+H)
10	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethyl-amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[(3-methoxy-propyl)amino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride	2or1	3-Methoxy-propylamine	2 hr.	602(M+H)
11	[7S-(7alpha,10aalpha)]-N-[9-(Aminocar-bonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetra-hydroxy-10,12-dioxo-2-naphthacenyl]-4-thiomorpholineacetamide dihydrochloride	2	Thiomorpholine	3 hr.	616(M+H)

Example #	Name	Starting Material of Exp. Prod.	Reactant	Rx Time	MS(FAB): m/z
12	[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-methyl-1-piperidineacetamide dihydrochloride	2	4-Methylpiperidine	2 hrs.	612(M+H)
13	[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-methyl-1-piperazineacetamide dihydrochloride	2	4-Methyl-1-piperazine	0.75 hr.	613(M+H)
14	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-9-[[(heptylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride	2	N-Heptylamine	2 hr.	628(M+H)
15	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(undecylamino)acetyl]amino]-2-naphthacenecarboxamide dihydrochloride	2	Undecylamine	3.5 hr.	684(M+H)
16	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(2-pyridinylmethyl)amino]acetyl]amido]-2-naphthacenecarboxamide dihydrochloride	2	2-(Aminomethyl) pyridine	1.5 hr.	621(M+H)

Example 17

[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydro-9-[[(2-hydroxyethyl)amino]acetyl]-amino]-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride

To a solution of 0.10 g of product from Example 7A in 2 ml of 1,3-dimethyl-2-imidazolidinone is added 0.70 ml of 2-amino-1-ethanol. The solution is stirred at room temperature for 20 minutes, added to 100 ml of diethyl ether and the resulting precipitate collected to give 0.055 g of the desired product.
MS(FAB):m/z 574 (M+H).

Substantially following the method described in detail hereinabove in Example 17, the compounds of this invention listed below in Examples 18-24 are prepared.

Example #	Name	Starting Material Prod. of Exp.	Reactant	Rx Time	MS(FAB): m/z
18	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[(2-hydroxyethyl)methylamino]acetyl]amino-1,11-dioxo-2-naphthacenecarboxamide	7A	4-methylamino-1-butanol	0.5 hrs.	588(M+H)
19	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[(4-(hydroxybutyl)amino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide	7A	4-amino-1-butanol	0.5 hr.	602(M+H)
20	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[2,2,2-trifluoroethyl)amino]-acetyl]amino]-2-naphthacenecarboxamide	7A	2,2,2-trifluoroethylamine	2 hr.	612(M+H)
21	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[[2-(1-piperidinyl)ethyl]amino]acetyl]-amino]-2-naphthacenecarboxamide	7A	1-(2-aminoethyl)pyrrolidine	2 hr.	627(M+H)

Example #	Name	Starting Material Prod. of Exp.	Reactant	Rx Time	MS(FAB): m/z
22	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[methyl-2-propynylamino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide	7A	N-methylpropargylamine	2 hrs.	581(M+H)
23	[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(1-piperidinylamino)acetyl]-amino]-2-naphthacenecarboxamide	7A	1-amino-piperidine	2 hrs.	613(M+H)

Example 24

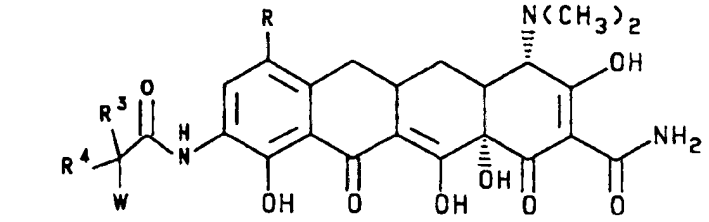
[4S-(4-alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(phenylmethoxy)-amino]acetyl]amino]-2-naphthacenecarboxamide

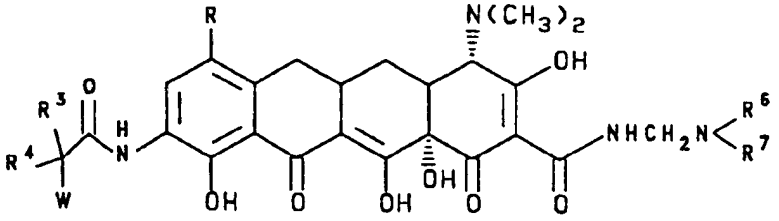
To 0.50 g of O-benzylhydroxylamine and 2.5 ml of 1,3-dimethyl-2-imidazolidinone is added 0.60 g of sodium bicarbonate. The mixture is stirred at room temperature for 2 hours, filtered and the filtrate added to 0.10 g of product from 7A. The reaction solution is stirred at room temperature for 2 hours and then added to 100 ml of diethyl ether. The resulting precipitate is collected and dried to give 0.90 g of the desired product

MS(FAB): m/z 636 (M+H)

Claims

1. A compound of the formula:





wherein:

R is a halogen selected from bromine, chlorine, fluorine and iodine; or R -NR^1R^2 and when R = -NR^1R^2 and R^1 = hydrogen,

R^2 = methyl, ethyl n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl; and when R^1 = methyl or ethyl,

R^2 = methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R^1 = n-propyl

R^2 = n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R^1 = 1-methylethyl,

R^2 = n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R^1 = n-butyl,

R^2 – n-butyl, 1-methylpropyl or 2-methylpropyl;

and when R^1 = 1-methylpropyl,

R^2 = 2-methylpropyl,

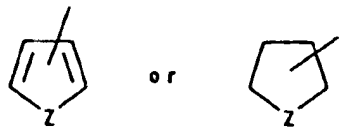
R^3 is selected from hydrogen; straight or branched (C_4-C_8)alkyl group selected from butyl, isobutyl, pentyl, hexyl, heptyl and octyl; α-mercapto(C_1-C_4)alkyl group selected from mercaptomethyl, α-mercaptoethyl, α-mercapto-1-methylethyl and α-mercaptopropyl;

α-hydroxy(C_1-C_4)alkyl group selected from hydroxymethyl, α-hydroxyethyl, α-hydroxy-1-methylethyl and α-hydroxypropyl; carboxyl(C_1-C_5)alkyl group;

(C_6-C_{10})aryl group selected from phenyl, α-naphthyl and β-naphthyl; substituted(C_6-C_{10})aryl group (substitution selected from hydroxy, halogen, (C_1-C_4)alkoxy, trihalo(C_1-C_3)alkyl, nitro amino cyano (C_1-C_4)alkoxycarbonyl,

(C_1-C_5)alkylamino and carboxy);
(C_7-C_9)aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl and phenylpropyl; substituted (C_7-C_9)aralkyl group [substitution selected from halo, (C_1-C_4)alkyl, nitro, hydroxy, amino, mono-or di-substituted (C_1-C_4) alkylamino, (C_1-C_4)alkoxy, (C_1-C_4)alkylsulfonyl, cyano and carboxy];
R^4 is selected from hydrogen and (C_1-C_6)alkyl selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl;
when R^3 does not equal R^4 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the substituent W) maybe be either the racemate (DL) or the individual enantiomers (L or D);
W is selected from hydroxylamino, (C_7-C_{12}) straight or branched alkyl monosubstituted amino group substitution selected from heptyl, octyl, nonyl, decyl, undecyl, dodecyl and the diastereomers and enantiomers of said branched alkyl monosubstituted amino group; (C_1-C_4) straight or branched fluoroalkylamino group selected from trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, 3,3,3,2,2-pentafluoropropyl, 2,2-difluoropropyl, 4,4,4-trifluorobutyl and 3,3-di-fluorobutyl; [(C_4-C_{10})cycloalkyl]alkyl monosubstituted amino group substitution selected from (cyclopropyl)methyl, (cyclopropyl)ethyl, (cyclobutyl)methyl, (trans-2-methylcyclopropyl)methyl, and (cis-2-methylcyclobutyl)methyl; (C_3-C_{10})alkenyl and alkynyl monosubstituted amino group substitution selected from allyl, 3-butenyl, 2-butenyl (cis or trans), 2-pentenyl, propynyl, 4-octenyl, 2,3-dimethyl-2-butenyl, 3-methyl-2-butenyl, 2-cyclopentenyl and 2-cyclohexenyl;
(C_7-C_{10})aralkylamino group substitution selected from benzyl, 2-phenylethyl, 1-phenylethyl, 2-(naphthyl)methyl, 1-(naphthyl)methyl and phenylpropyl; substituted (C_6-C_{10})aryl monosubstituted amino group [substitution selected from (C_1-C_5)acyl, (C_1-C_5)acylamino, (C_1-C_4)alkyl, mono or disubstituted (C_1-C_8)alkylamino, (C_1-C_4)alkoxy, (C_1-C_4)alkoxycarbonyl, (C_1-C_4)alkylsulfonyl, amino, carboxy, cyano, halogen, hydroxy, nitro and trihalo(C_1-C_3)alkyl]; straight or branched symmetrical disubstituted alkylamino group substitution selected from dibutyl, diisobutyl, di-s-butyl, dipentyl, diisopentyl, di-s-pentyl, dihexyl, diisohexyl and di-s-hexyl; symmetrical disubstituted (C_6--C_{14}) cycloalkyl-amino group substitution selected from dicyclopropyl, dicyclobutyl, dicyclopentyl, di(dicyclopropyl)methyl, dicyclohexyl and dicycloheptyl;
straight or branched unsymmetrical disubstituted (C_3--C_{14})alkylamino group wherein the total number of carbons in the substitution is more than 14;
unsymmetrical disubstituted (C_4-C_{14})cycloalkylamino group wherein the total number of carbons in the substitution is no more than 14; (C_2-C_8)azacycloalkyl and substituted (C_2-C_8)azacycloalkyl group substitution selected from 4-methylpiperidinyl, 4-hydroxypiperidinyl, 4-(hydroxymethyl)piperidinyl, 4-(aminomethyl)piperidinyl, cis-3,4-dimethylpyrrolidinyl, trans-3,4-dimethylpyrrolidinyl, 2-azabicyclo [2.1.1]hex-2-yl, 5-azabicyclo[2.1.1]hex-5-yl, 2-azabicyclo[2.2.1]hept-2-yl, 7-azabicyclo[2.2.1]hept-7-yl, 2-azabicyclo[2.2.2]oct-2-yl and the diastereomers and enantiomers of said (C_2-C_8)azacycloalkyl and substituted (C_2-C_8)azacycloalkyl group; substituted 1-azaoxacycloalkyl group substitution selected from 2-(C_1-C_3)alkylmorpholinyl, 3-(C_1-C_3)alkylisoxazolidinyl, tetrahydrooxazinyl and 3,4-dihydrooxazinyl; [1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group selected from piperazinyl, 2-(C_1--C_3)alkylpiperazinyl, 4-(C_1-C_3)alkylpiperazinyl, 2,4-dimethylpiperazinyl, 4-(C_1-C_4)alkoxypiperazinyl, 4-(C_6-C_{10})aryloxypiperazinyl, 4-hydroxypiperazinyl, 2,5-diazabicyclo[2.2.1]hept-2-yl, 2,5-diaza-5-methylbicyclo [2.2.1]hept-2-yl, 2,3-diaza-3-methylbicyclo[2.2.2]oct-2-yl, 2,5-diaza-5,7-dimethylbicyclo[2.2.2]oct-2-yl and the diastereomers or enantiomers of said [1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group; 1-azathiacycloalkyl and substituted 1-azathiacycloalkyl group selected from thiomorpholinyl, 2-(C_1-C_3)alkylthiomorpholinyl and 3-(C_3-C_6)cycloalkylthiomorpholinyl; N-azolyl and substituted N-azolyl group selected from 1-imidazolyl, 2-(C_1-C_3)alkyl-1-imidazolyl, 3-(C_1-C_3)alkyl-1-imidazolyl, 1-pyrrolyl, 2-(C_1-C_3)alkyl-1-pyrrolyl, 3-(C_1-C_3)alkyl-1-pyrrolyl, 1-pyrazolyl, 3-(C_1-C_3)alkyl-1-pyrazolyl, indolyl, 1-(1,2,3-triazolyl), 4-(C_1-C_3)alkyl-1-(1,2,3-triazolyl), 5-(C_1-C_3)alkyl-1-(1,2,3-triazolyl), 4-(1,2,4-triazolyl, 1-tetrazolyl, 2-tetrazolyl and benzimidazolyl;
(heterocycle)amino group said heterocycle selected from 2- or 3-furanyl, 2- or 3-thienyl, 2-,3- or 4-pyridyl, 2- or 5-pyridazinyl, 2-pyrazinyl, 2-(imidazolyl), (benzimidazolyl), and (benzothiazolyl) and substituted (heterocycle)amino group (substitution selected from straight or branched (C_1--C_6)alkyl); (heterocycle)methylamino group selected from 2- or 3-furylmethylamino, 2- or 3-thienylmethyl-amino, 2-, 3- or 4-pyridylmethylamino, 2- or 5-pyridazinylmethylamino, 2-pyrazinylmethylamino, 2-(imidazolyl)methylamino, (benzimidazolyl)methylamino, and (benzothiazolyl) methylamino and said substituted (heterocycle)methylamino group (substitution selected from straight or branched (C_1-C_6)alkyl); carboxy(C_2-C_4)alkylamino group selected from aminoacetic acid, α-aminopropionic acid, β-aminopropionic acid, α-aminobutyric acid, β-aminobutyric acid and the enantiomers of said carboxy(C_2-C_4)alkylamino group; 1,1-disubstituted hydrazino group selected from 1,1-dimethylhydrazino, N-aminopiperidinyl, 1,1-diethylhydrazino, and N-aminopyrrolidinyl; (C_1-C_4)-alkoxyamino group substitution selected from methoxy, ethoxy, n-propoxy, 1-methylethoxy, n-butoxy, 2-methylpropoxy and 1,1-dimethylethoxy; (C_3-C_8)cycloalkoxyamino group selected from cyclopropoxy, trans-1,2-dimethylcyclopropoxy, cis-1,2-dimethylcyclopropoxy, cyclobutoxy, cyclopentoxy, cyclohexoxy, cycloheptoxy, cyclooctoxy, bicyclo[2.2.1]hept-2-yloxy, bicyclo[2.2.2]oct-2-yloxy and the diastereomers and enantiomers of said (C_3-C_8)cycloalkoxyamino group; (C_6-C_{10})aryloxyamino group selected from phe-

noxyamino, 1-naphthyloxyamino and 2-naphthyloxyamino; (C_7-C_{11})-arylalkoxyamino group substitution selected from benzyloxy, 2-phenylethoxy, 1-phenylethoxy, 2-(naphthyl)methoxy, 1-(naphthyl)methoxy and phenylpropoxy; [β or γ-(C_1-C_3)acylamido]alkylamino group substitution selected from 2-(formamido)ethyl, 2-(acetamido)ethyl, 2-(propionylamido)ethyl, 2-(acetamido)propyl, 2-(formamido)propyl and the enantiomers of said [β or γ-(C_1-C_3)acylamido]alkylamino group; β or γ-(C_1-C_3)alkoxyalkylamino group substitution selected from 2-methoxyethyl, 2-ethoxyethyl, 2,2-diethoxyethyl, 2-methoxypropyl, 3-methoxypropyl, 3-ethoxypropyl, 3,3-diethoxypropyl and the enantiomers of said β or γ-(C_1-C_3)alkoxyalkylamino group; β,γ or δ (C_2-C_4)hydroxyalkylamino group substitution selected from 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl and 4-hydroxybutyl;
or R^3 and W taken together are selected from $-(CH_2)_n(R^5)N-$, n= 3 - 4, and $-CH_2CH(OH)CH_2(R^5)N-$ wherein R^5 is selected from hydrogen and (C_1-C_3)acyl, the acyl selected from formyl, acetyl, propionyl and (C_2-C_3)haloacyl selected from chloroacetyl, bromoacetyl, trifluoroacetyl, 3,3,3-trifluoropropionyl and 2,3,3-trifluoropropionyl;
R^6 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (C_6-C_{10})aryl group selected from phenyl, α-naphthyl or β-naphthyl; (C_7-C_9)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:

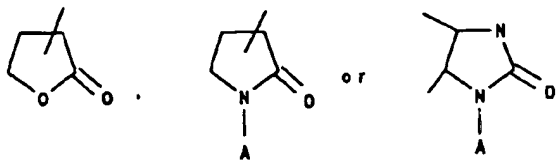


Z - N, O, S or Se

such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O, S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:

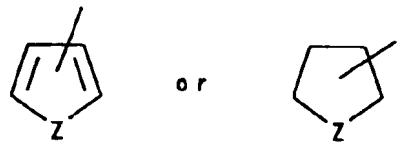
Z or Z^1 - N, O, S or Se

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazo[4,5-b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



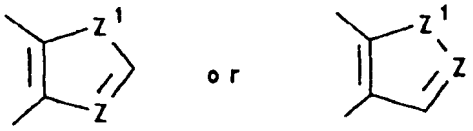
(A is selected from hydrogen; straight or branched (C_1-C_4)alkyl; C_6-aryl; substituted C_6-aryl (substitution selected from halo,(C_1-C_4)alkoxy, trihalo(C_1-C_3)alkyl, nitro, amino, cyano, (C_1-C_4)-alkoxycarbonyl, (C_1-C_3)alkylamino or carboxy); (C_7-C_9)-aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)
such as γ-butyrolactam, γ-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, sym-triazinyl, unsym-triazinyl, pyrimidinyl or (C_1-C_3) alkylthiopyridazinyl, or a six membered saturated ring with one or two N, O, S or Se heteroatoms

and an adjacent appended O hetercatom such as 2,3-dioxo-1-piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1-piperazinyl, 2-dioxomorpholinyl, 2-dioxothiomorpholinyl; or $-(CH_2)_nCOOR^8$ where n=0-4 and R^8 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; or (C_6-C_{10})aryl group selected from phenyl, α-naphthyl, or β-naphthyl; R^7 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; (C_6-C_{10})aryl group selected from phenyl, α-naphthyl or β-naphthyl; (C_7-C_9)aralkyl group such as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl; a heterocycle group selected from a five membered aromatic or saturated ring with one N, O, S or Se heteroatom optionally having a benzo or pyrido ring fused thereto:



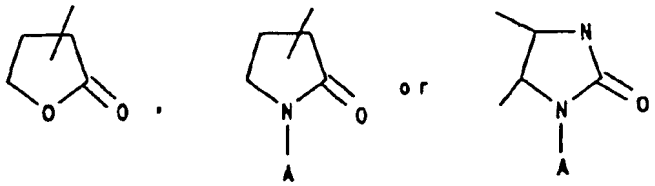
Z = N, O, S or Se

such as pyrrolyl, N-methylindolyl, indolyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyrrolinyl, tetrahydrofuranyl, furanyl, benzofuranyl, tetrahydrothienyl, thienyl, benzothienyl or selenazolyl, or a five membered aromatic ring with two N, O S or Se heteroatoms optionally having a benzo or pyrido ring fused thereto:



Z or Z^1 = N, O, S or Se

such as imidazolyl, pyrazolyl, benzimidazolyl, oxazolyl, benzoxazolyl, indazolyl, thiazolyl, benzothiazolyl, 3-alkyl-3H-imidazo[4,5-b]pyridyl or pyridylimidazolyl, or a five membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom:



(A is selected from hydrogen; straight or branched (C_1-C_4)alkyl; C_6-aryl; substituted C_6-aryl (substitution selected from halo,(C_1-C_4)alkoxy, trihalo(C_1-C_3)alkyl, nitro, amino, cyano, (C_1-C_4)-alkoxycarbonyl, (C_1-C_3)alkylamino or carboxy); (C_7-C_9)-aralkyl group selected from benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl)
such as γ-butyrolactam, γ-butyrolactone, imidazolidinone or N-aminoimidazolidinone, or a six membered aromatic ring with one to three N heteroatoms such as pyridyl, pyridazinyl, pyrazinyl, sym-triazinyl, unsym-triazinyl, pyrimidinyl or (C_1-C_3)alkylthiopyridazinyl or a six membered saturated ring with one or two N, O, S or Se heteroatoms and an adjacent appended O heteroatom such as 2,3-dioxo-1-piperazinyl, 4-ethyl-2,3-dioxo-1-piperazinyl, 4-methyl-2,3-dioxo-1-piperazinyl, 4-cyclopropyl-2-dioxo-1-piperazinyl, 2-dioxomorpholinyl, 2-dioxothiomorpholinyl; or $-(CH_2)_nCOOR^8$ where n=0-4 and R^8 is selected from hydrogen; straight or branched (C_1-C_3)alkyl selected from methyl, ethyl, n-propyl or 1-methylethyl; or (C_6-C_{10})aryl selected from phenyl, α-naphthyl or β-naphthyl; with the proviso that R^6 and R^7 cannot both be hydrogen;
or R^6 and R^7 taken together are $-(CH_2)_2B(CH_2)_2-$, wherein B is selected from $(CH_2)_n$ and n=0-1, -NH, $-N(C_1-C_3)$

alkyl [straight or branched], -N(C_1-C_4)alkoxy, oxygen, sulfur or substituted congeners selected from (L or D)proline, ethyl(L or D)prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts or metal complexes, with the proviso that when R^3 and R^4 both represent hydrogen then W is other than benzylamino, 1-imidazolyl, 1-pyrrolyl, 1-(1,2,3-triazolyl) or 4-(1,2,4-triazolyl).

2. The compound according to Claim 1, wherein:
R is a halogen selected from bromine, chlorine and iodine; or R = -NR^1R^2
and when R = -NR^1R^2 and R^1 = methyl or ethyl,
R^2 = methyl or ethyl,
R^3 is selected from hydrogen;
R^4 is selected from hydrogen and (C_1-C_2)alkyl selected from methyl and ethyl,
when R^3 does not equal R^4 the stereochemistry of the asymmetric carbon (i.e. the carbon bearing the substituent W) maybe be either the racemate (DL) or the individual enantiomers (L or D);
W is selected from (C_7-C_{12}) straight or branched alkyl monosubstituted amino group substitution selected from heptyl, octyl, nonyl, decyl, undecyl, dodecyl and the diastereomers and enantiomers of said branched alkyl monosubstituted amino group; (C_2)fluoroalkylamino group selected from 2,2,2-trifluoroethyl and 3,3,3-trifluoropropyl; [(C_4-C_5)cycloalkyl]alkyl monosubstituted amino group substitution selected from (cyclopropyl)methyl and (cyclopropyl)ethyl; (C_3-C_4)alkenyl and alkynyl monosubstituted amino group substitution selected from allyl and propynyl; (C_2-C_7)azacycloalkyl and substituted (C_2-C_7)azacycloalkyl group substitution selected from 4-methylpiperidinyl, 4-hydroxypiperidinyl and 4-(hydroxymethyl)piperidinyl; substituted 1-azaoxacycloalkyl group substitution selected from 2-(C_1-C_3)alkylmorpholinyl;
[1,n]-diazacycloalkyl and substituted [1,n]-diazacycloalkyl group selected from piperazinyl and 4-(C_1-C_3)alkylpiperazinyl;
1-azathiacycloalkyl and substituted 1-azathiacycloalkyl group selected from thiomorpholinyl and 2-(C_1-C_3)-alkylthiomorpholinyl; (heterocyclo)methylamino group selected from 2- or 3-thienylmethylamino and 2-, 3- or 4-pyridylmethylamino; 1,1-disubstituted hydrazino group selected from 1,1-dimethylhydrazino and N-amino-piperidinyl. [β or γ-(C_1-C_3)acylamido]alkylamino group substitution selected from 2-(acetamido)ethyl; β or γ-(C_1-C_3)alkoxyalkylamino group substitution selected from 2-methoxyethyl, 2-ethoxyethyl, 2,2-diethoxyethyl, 2-methoxypropyl and 3-methoxypropyl; β, γ or δ (C_2-C_4)-hydroxyalkylamino selected from 4-hydroxybutyl and 3-hydroxypropyl; or R^3 and W taken together are selected from -$(CH_2)_n(R^5)N$-, n= 3, and R^5 is selected from hydrogen and trifluoroacetyl;
R^6 is selected from hydrogen; straight or branched (C_1-C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl;
R^7 is selected from hydrogen; straight or branched (C_1--C_3)alkyl group selected from methyl, ethyl, n-propyl or 1-methylethyl; with the proviso that R_6 and R_7 cannot both be hydrogen;
or R^6 and R^7 taken together are -$(CH_2)_2B(CH_2)_2$-, wherein B is selected from $(CH_2)_n$ and n=0-1, -NH, -N(C_1-C_3) alkyl [straight or branched], -N(C_1-C_4)alkoxy, oxygen, sulfur or substituted congeners selected from (L or D)proline, ethyl(L or D)prolinate, morpholine, pyrrolidine or piperidine; and the pharmacologically acceptable organic and inorganic salts or metal complexes.

3. The compound according to Claims 1 or 2 wherein said salts or complexes comprise: hydrochloric, hydrobromic hydroiodic, phosphoric, nitric, sulfate, acetate, benzoate, citrate, cysteine, fumarate, glycolate, maleate, succinate, tartrate, alkylsulfonate, arylsulfonate, aluminum, calcium, iron, magnesium or manganese.

4. A compound according to Claim 1,

[4S-(4alpha,12aalpha)]-9-[[[(Cyclopropylmethyl)amino]-acetyl]amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a, 6,11, 12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride;

[4S-(4alpha,12aalpha)]-9-[[[(2,2-diethoxyethyl)amino]-acetyl]amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a, 6,11,-12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride;

[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,-5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[2-(methoxyethyl)amino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride;

[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,-5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(2-propenylamino)acetyl]amino]-2-naphthacenecarboxamide dihydrochloride.

[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,-5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[(3-methoxypropyl)amino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride;

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,7-bis-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,-10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-thiomorpholineacetamide dihydrochloride;

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,7-bis-(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,-10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-methyl-1-piperidineacetamide dihydrochloride,

[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,-10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-methyl-1-piperazineacetamide dihydrochloride.

[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-9-[[(heptylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide dihydrochloride;

[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,-5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(undecylamino)acetyl]amino]-2-naphthacene-carboxamide dihydrochloride;

[4S-(4alpha,12aalpha)]-4,7-bis(dimethylamino)-1,4,4a,-5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(2-pyridinylmethyl)amino]acetyl]amido]-2-naphthacenecarboxamide dihydrochloride,

[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4, 4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[(2-hydroxyethyl)amino]acetyl]-amino]-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride;

[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,-5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[(2-hydroxyethyl)methylamino]acetyl]amino-1,11-dioxo-2-naphthacenecarboxamide;

[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,-5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[(4-(hydroxybutyl)amino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide;

[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,-5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[2,2,2-trifluoroethyl)amino]acetyl]amino]-2-naphthacenecarboxamide;

[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,-5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[2-(1-piperidinyl)ethyl]amino]acetyl]amino]-2-naphthacenecarboxamide;

[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,-5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[methyl-2-propynylamino]acetyl]amino]-1,11-dioxo-2-naphthacenecarboxamide;

[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,-5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(1-piperidinylamino)acetyl]amino]-2-naphthacenecarboxamide; or

[4S-(4-alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(phenylmethoxy)-amino]acetyl]amino]-2-naphthacenecarboxamide

5. A compound according to Claim 1 for use in a method for the prevention or control of bacterial infections in warm blooded animals.

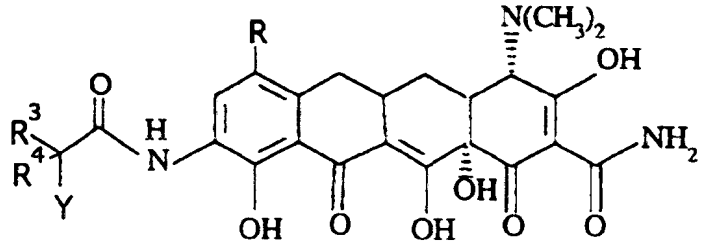
6. A pharmaceutical composition of matter comprising a pharmacologically effective amount of a compound according to Claim 1 in association with a pharmaceutically acceptable carrier.

7. A veterinary composition which comprises a pharmacologically effective amount of a compound of Claim 1 and a pharmaceutically acceptable carrier.

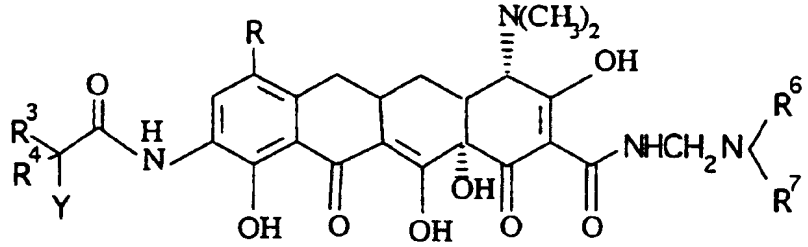
8. A compound according to Claim 1 for use in a method for the prevention, treatment or control of bacterial infections in warm-blooded animals caused by bacteria having the TetM and TetK resistant determinants.

9. A method of producing a compound of the formula I as claimed in Claim 1 which comprises reacting a corresponding

9-[(haloacyl)amido]-7-(substituted)-6-demethyl-6-deoxytetracycline, or an organic or inorganic salt or metal complex, of the formula:



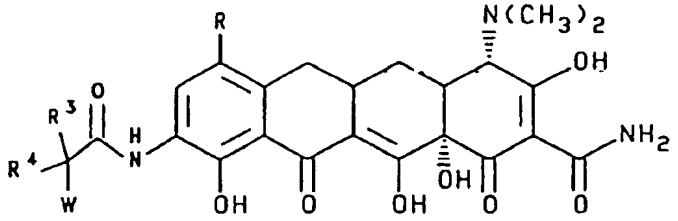
or

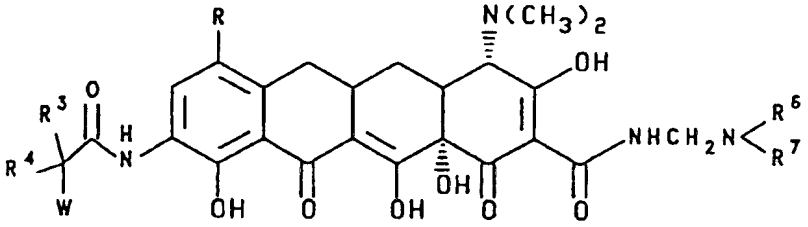


wherein Y is chlorine, bromine, fluorine or iodine, with a nucleophile of the formula WH, wherein W is as defined in Claim 1, in a polar- aprotic solvent and in an inert atmosphere.

Patentansprüche

1. Verbindung der Formel





worin R ein Halogen ist, ausgewählt aus Brom, Chlor, Fluor und Jod; oder R = -NR^1R^2, und wenn R = -NR^1R^2 und R^1 = Wasserstoff, R^2 = Methyl, Ethyl, n-Propyl, 1-Methylethyl, n-Butyl, 1-Methylpropyl, 2-Methylpropyl oder 1,1-Dimethylethyl; und wenn R^1 = Methyl oder Ethyl, R^2 = Methyl, Ethyl, n-Propyl, 1-Methylethyl, n-Butyl, 1-Methylpropyl

oder 2-Methylpropyl; und wenn R^1 = n-Propyl, R^2 = n-Propyl, 1-Methylethyl, n-Butyl, 1-Methylpropyl oder 2-Methylpropyl; und wenn R^1 = 1-Methylethyl, R^2 = n-butyl, 1-Methylpropyl oder 2-Methylpropyl; und wenn R^1 = n-Butyl, R^2 = n-Butyl, 1-Methylpropyl oder 2-Methylpropyl; und wenn R^1 = 1-Methylpropyl, R^2 = 2-Methylpropyl; R^3 ist ausgewählt aus Wasserstoff; gerader oder verzweigter (C_4-C_8)-Alkylgruppe, ausgewählt aus Butyl, Isobutyl, Pentyl, Hexyl, Heptyl und Octyl; α-Mercapto(C_1-C_4)-alkylgruppe, ausgewählt aus Mercaptomethyl, α-Mercaptoethyl, α-Mercapto-1-methylethyl und α-Mercaptopropyl; α-Hydroxy(C_1-C_4)-alkylgruppe, ausgewählt aus Hydroxymethyl, α-Hydroxyethyl, α-Hydroxy-1-methylethyl und α-Hydroxypropyl; Carboxyl(C_1-C_8)-alkylgruppe; (C_6-C_{10})-Arylgruppe, ausgewählt aus Phenyl, α-Naphthyl und β-Naphthyl; substituierte (C_6-C_{10})-Arylgruppe (Substitution ausgewählt aus Hydroxy, Halogen, (C_1-C_4)-Alkoxy, Trihalo(C_1-C_3)-alkyl, Nitro, Amino, Cyano, (C_1-C_4)-Alkoxycarbonyl, (C_1-C_3)-Alkylamino und Carboxy); (C_7-C_9)-Aralkylgruppe, ausgewählt aus Benzyl, 1-Phenylethyl, 2-Phenylethyl und Phenylpropyl; substituierte (C_7-C_9)-Aralkylgruppe [Substitution ausgewählt aus Halo, (C_1-C_4)-Alkyl, Nitro, Hydroxy, Amino, mono- oder disubstituiertes (C_1-C_4)-Alkylamino, (C_1-C_4)-Alkoxy, (C_1-C_4)-Alkylsulfonyl, Cyano und Carboxy]; R^4 ist ausgewählt aus Wasserstoff und (C_1-C_6)-Alkyl, ausgewählt aus Methyl, Ethyl, Propyl, Isopropyl, Butyl, Isobutyl, Pentyl und Hexyl; wenn R^3 nicht gleich R^4 ist, kann die Stereochemie des asymmetrischen Kohlenstoffs (d.h. des Kohlenstoffs, der den Substituenten W tragt) entweder das Razemat (DL) oder die einzelnen Enantiomere (L oder D) sein; W ist ausgewählt aus Hydroxylamino; gerade oder verzweigte (C_7-C_{12}-)Alkyl-monosubstituierte Aminogruppe, wobei die Substitution aus Heptyl, Octyl, Nonyl, Decyl, Undecyl, Dodecyl und den Diastereomeren und Enantiomeren dieser verzweigten Alkyl-monosubstituierten Aminogruppe ausgewählt ist; gerade oder verzweigte (C_1-C_4-)Fluoralkylaminogruppe, ausgewählt aus Trifluormethyl, 2,2,2-Trifluorethyl, 3,3,3-Trifluorpropyl, 3,3,3,2,2-Pentafluorpropyl, 2,2-Difluorpropyl, 4,4,4-Trifluorbutyl und 3,3-Difluorbutyl; [(C_4-C_{10})-Cycloalkyl]alkyl-monosubstituierte Aminogruppe, wobei die Substitution aus (Cyclopropyl)methyl, (Cyclopropyl)ethyl, (Cyclobutyl)methyl, (trans-2-Methylcyclopropyl)methyl und (cis-2-Methylcyclobutyl)methyl ausgewählt ist; (C_3-C_{10})-Alkenyl- und Alkinyl-monosubstituierte Aminogruppe, wobei die Substitution aus Allyl, 3-Butenyl, 2-Butenyl (cis oder trans), 2-Pentenyl, Propinyl, 4-Octenyl, 2,3-Dimethyl-2-butenyl, 3-Methyl-2-butenyl, 2-Cyclopentenyl und 2-Cyclohexenyl ausgewählt ist; (C_7-C_{10})-Aralkylaminogruppe, wobei die Substitution aus Benzyl, 2-Phenylethyl, 1-Phenylethyl, 2-(Naphthyl)methyl, 1-(Naphthyl)methyl und Phenylpropyl ausgewählt ist; substituiertes (C_6-C_{10})-Aryl-monosubstituierte Aminogruppe [Substitution ausgewählt aus (C_1-C_5)-Acyl, (C_1-C_5)-Acylamino, (C_1-C_4)-Alkyl, mono- oder disubstituiertes (C_1-C_8)-Alkylamino, (C_1-C_4)-Alkoxy, (C_1-C_4)-Alkoxycarbonyl, (C_1-C_4)-Alkylsulfonyl, Amino, Carboxy, Cyano, Halogen, Hydroxy, Nitro und Trihalo(C_1-C_3)-Alkyl]; gerade oder verzweigte symmetrische disubstituierte Alkylaminogruppe, wobei die Substitution aus Dibutyl, Diisobutyl, Di-s-butyl, Dipentyl, Diisopentyl, Di-s-pentyl, Dihexyl, Diisohexyl und Di-s-hexyl ausgewählt ist; symmetrische disubstituierte (C_6-C_{14})-Cycloalkylaminogruppe, wobei die Substitution aus Dicyclopropyl, Dicyclobutyl, Dicyclopentyl, Di(dicyclopropyl)methyl, Dicyclohexyl und Dicycloheptyl ausgewählt ist; gerade oder verzweigte asymmetrische disubstituierte (C_3-C_{14})-Alkylaminogruppe, worin die Gesamtzahl der Kohlenstoffe in der Substitution größer ist als 14; asymmetrische disubstituierte (C_4-C_{14})-Cycloalkylaminogruppe, worin die Gesamtzahl der Kohlenstoffe in der Substitution nicht größer ist als 14; (C_2-C_8)-Azacycloalkyl- und substituierte (C_2-C_8)-Azacycloalkylgruppe, wobei die Substitution aus 4-Methylpiperidinyl, 4-Hydroxypiperidinyl, 4-(Hydroxymethyl)piperidinyl, 4-(Aminomethyl)piperidinyl, cis-3,4-Dimethylpyrrolidinyl, trans-3,4-Dimethylpyrrolidinyl, 2-Azabicyclo[2.1.1]hex-2-yl, 5-Azabicyclo[2.1.1]hex-5-yl, 2-Azabicyclo[2.2.1]hept-2-yl, 7-Azabicyclo[2.2.1]hept-7-yl, 2-Azabicyclo[2.2.2]oct-2-yl und den Diastereomeren und Enantiomeren dieser (C_2-C_8)-Azacycloalkyl- und substituierten (C_2-C_8)-Azacycloalkylgruppe ausgewählt ist; substituierte 1-Azaoxacycloalkylgruppe, wobei die Substitution aus 2-(C_1-C_3)-Alkylmorpholinyl, 3-(C_1-C_3)-Alkylisoxazolidinyl, Tetrahydrooxazinyl und 3,4-Dihydrooxazinyl ausgewählt ist; [1,n]-Diazacycloalkyl- und substituierte [1,n]-Diazacycloalkylgruppe, ausgewählt aus Piperazinyl, 2-(C_1-C_3)-Alkylpiperazinyl, 4-(C_1-C_3)-Alkylpiperazinyl, 2,4-Dimethylpiperazinyl, 4-(C_1-C_4)-Alkoxypiperazinyl, 4-(C_6-C_{10})-Aryloxypiperazinyl, 4-Hydroxypiperazinyl, 2,5-Diazabicyclo[2.2.1]hept-2-yl, 2,5-Diaza-5-methylbicyclo-[2.2.1]hept-2-yl, 2,3-Diaza-3-methylbicyclo[2.2.2]oct-2-yl, 2,5-Diaza-5,7-dimethyl-bicyclo[2.2.2]oct-2-yl und den Diastereomeren und Enantiomeren dieser [l,n]-Diazacycloalkyl- und substituierten [1,n]-Diazacycloalkylgruppe; 1-Azathiacycloalkyl- und substituierte 1-Azathiacycloalkylgruppe, ausgewählt aus Thiomorpholinyl, 2-(C_1-C_3)-Alkylthiomorpholinyl und 3-(C_3-C_6)-Cycloalkylthiomorpholinyl; N-Azolyl- und substituierte N-Azolylgruppe, ausgewählt aus 1-Imidazolyl, 2-(C_1-C_3)-Alkyl-1-imidazolyl, 3-(C_1-C_3)-Alkyl-1-imidazolyl, 1-Pyrrolyl, 2-(C_1-C_3)-Alkyl-1-pyrrolyl, 3-(C_1-C_3)-Alkyl-1-pyrrolyl, 1-Pyrazolyl, 3-(C_1-C_3)-Alkyl-1-pyrazolyl, Indolyl, 1-(1,2,3-Triazolyl), 4-(C_1-C_3)-Alkyl-1-(1,2,3-triazolyl), 5-(C_1-C_3)-Alkyl-1-(1,2,3-triazolyl), 4-(1,2,4-Triazolyl, 1-Tetrazolyl, 2-Tetrazolyl und Benzimidazolyl; (Heterocyclus-)Aminogruppe, wobei dieser Heterocyclus aus 2- oder 3-Furanyl, 2- oder 3-Thienyl, 2-, 3- oder 4-Pyridyl, 2- oder 5-Pyridazinyl, 2-Pyrazinyl, 2-(Imidazolyl), (Benzimidazolyl) und (Benzothiazolyl) und substituierter (Heterocyclus-)Aminogruppe (Substitution ausgewählt aus geradem oder verzweigtem (C_1-C_6)-Alkyl) ausgewählt ist; (Heterocyclus-)Methylaminogruppe, ausgewählt aus 2- oder 3-Furylmethylamino, 2- oder 3-Thienylmethylamino, 2-, 3- oder 4-Pyridylmethylamino, 2- oder 5-Pyridazinylmethylamino, 2-Pyrazinylmethylamino, 2-(Imidazolyl)methylamino, (Benzimidazolyl)methylamino und (Benzothiazolyl)methylamino und diese substituierte (Heterocyclus-)Methylaminogruppe (Substitution aus-

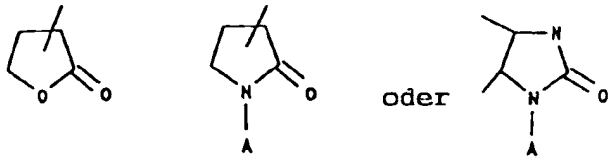
gewählt aus geradem oder verzweigtem (C_1-C_6)-Alkyl; Carboxy(C_2-C_4)-Alkylaminogruppe, ausgewählt aus Aminoessigsäure, α-Aminopropionsäure, β-Aminopropionsäure, α-Aminobuttersäure, β-Aminobuttersäure und den Enantiomeren dieser Carboxy(C_2-C_4)-Alkylaminogruppe; 1,1-disubstituierte Hydrazingruppe, ausgewählt aus 1,1-Dimethylhydrazin, N-Aminopiperidinyl, 1,1-Diethylhydrazin und N-Aminopyrrolidinyl; (C_1-C_4)-Alkoxyaminogruppe, wobei die Substitution aus Methoxy, Ethoxy, n-Propoxy, 1-Methylethoxy, n-Butoxy, 2-Methylpropoxy und 1,1-Dimethylethoxy ausgewählt ist; (C_3-C_8)-Cycloalkoxyaminogruppe, ausgewählt aus Cyclopropoxy, trans-1,2-Dimethylcyclopropoxy, cis-1,2-Dimethylcyclopropoxy, Cyclobutoxy, Cyclopentoxy, Cyclohexoxy, Cycloheptoxy, Cyclooctoxy, Bicyclo[2.2.1]hept-2-yloxy, Bicyclo[2.2.2]oct-2-yloxy und den Diastereomeren und Enantiomeren dieser (C_3-C_8)-Cycloalkoxyaminogruppe; (C_6-C_{10}-)Aryloxyaminogruppe, ausgewählt aus Phenoxyamino, 1-Naphthyloxyamino und 2-Naphthyloxyamino; (C_7-C_{11})-Arylalkoxyaminogruppe, wobei die Substitution aus Benzyloxy, 2-Phenylethoxy, 1-Phenylethoxy, 2-(Naphthyl)methoxy, 1-(Naphthyl)methoxy und Phenylpropoxy ausgewählt ist; [β- oder γ-(C_1-C_3)-Acylamido]alkylaminogruppe, wobei die Substitution aus 2-(Formamido)ethyl, 2-(Acetamido)ethyl, 2-(Propionylamido)ethyl, 2-(Acetamido)propyl, 2-(Formamido)propyl und den Enantiomeren dieser [β- oder γ-(C_1-C_3)-Acylamido]alkylaminogruppe ausgewählt ist; β- oder γ-(C_1-C_3)Alkoxyalkylaminogruppe, wobei die Substitution aus 2-Methoxyethyl, 2-Ethoxyethyl, 2,2-Diethoxyethyl, 2-Methoxypropyl, 3-Methoxypropyl, 3-Ethoxypropyl, 3,3-Diethoxypropyl und den Enantiomeren dieser β- oder γ-(C_1-C_3)-Alkoxyalkylaminogruppe ausgewählt ist, β-, γ- oder δ-(C_2-C_4)-Hydroxyalkylaminogruppe, wobei die Substitution aus 2-Hydroxyethyl, 2-Hydroxypropyl, 3-Hydroxypropyl und 4-Hydroxybutyl ausgewählt ist; oder R^3 und W zusammengenommen sind ausgewählt aus $-(CH_2)_n(R^5)N-$, n = 3-4, und $-CH_2CH(OH)CH_2(R^5)N-$, worin R^5 aus Wasserstoff und (C_1-C_3)-Acyl ausgewählt ist, wobei das Acyl ausgewählt ist aus Formyl, Acetyl, Propionyl und (C_2-C_3)-Haloacyl, ausgewählt aus Chloracetyl, Bromacetyl, Trifluoracetyl, 3,3,3-Trifluorpropionyl und 2,3,3-Trifluorpropionyl; R^6 ist ausgewählt aus Wasserstoff; gerader oder verzweigter (C_1-C_3)-Alkylgruppe, ausgewählt aus Methyl, Ethyl, n-Propyl oder 1-Methylethyl; (C_6-C_{10})-Arylgruppe, ausgewählt aus Phenyl, α-Naphthyl oder β-Naphthyl; (C_7-C_9)-Aralkylgruppe, wie Benzyl, 1-Phenylethyl, 2-Phenylethyl oder Phenylpropyl; eine Heterocyclus-Gruppe, ausgewählt aus einem 5-gliedrigen aromatischen oder gesättigten Ring mit einem N-, O-, S- oder Se-Heteroatom, gegebenenfalls mit einem daran kondensierten Benzo- oder Pyrido-Ring:

Z = N, O, S oder Se

wie Pyrrolyl, N-Methylindolyl, Indolyl, 2-Pyrrolidinyl, 3-Pyrrolidinyl, 2-Pyrrolinyl, Tetrahydrofuranyl, Furanyl, Benzofuranyl, Tetrahydrothienyl, Thienyl, Benzothienyl oder Selenazolyl, oder ein 5-gliedriger aromatischer Ring mit zwei N-, O-, S- oder Se-Heteroatomen, gegebenenfalls mit einem daran kondensierten Benzo- oder Pyrido-Ring:

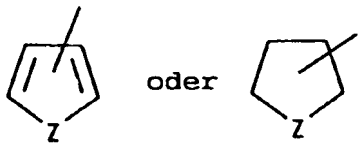
Z oder Z^1 = N, O, S oder Se

wie Imidazolyl, Pyrazolyl, Benzimidazolyl, Oxazolyl, Benzoxazolyl, Indazolyl, Thiazolyl, Benzothiazolyl, 3-Alkyl-3H-imidazo-[4,5-b]pyridyl oder Pyridylimidazolyl, oder ein 5-gliedriger gesättigter Ring mit einem oder zwei N-, O-, S- oder Se-Heteroatomen und einem benachbarten angehängten O-Heteroatom:



(A ist ausgewählt aus Wasserstoff; geradem oder verzweigtem (C_1-C_4)-Alkyl; C_6-Aryl; substituiertem C_6-Aryl (Substitution ausgewählt aus Halo, (C_1-C_4)-Alkoxy, Trihalo(C_1-C_3)-Alkyl, Nitro, Amino, Cyano, (C_1-C_4)-Alkoxycarbonyl, (C_1-C_3)-Alkylamino oder Carboxy); (C_7-C_9)-Aralkylgruppe, ausgewählt aus Benzyl, 1-Phenylethyl, 2-Phenylethyl oder Phenylpropyl)

wie γ-Butyrolactam, γ-Butyrolacton, Imidazolidinon oder N-Aminoimidazolidinon, oder ein 6-gliedriger aromatischer Ring mit einem oder drei N-Heteroatomen, wie Pyridyl, Pyridazinyl, Pyrazinyl, sym-Triazinyl, asym-Triazinyl, Pyrimidinyl oder (C_1-C_3)-Alkylthiopyridazinyl, oder ein 6-gliedriger gesättigter Ring mit einem oder zwei N- O-, S- oder Se-Heteroatomen und einem benachbarten angehängten O-Heteroatom, wie 2,3-Dioxo-1-piperazinyl, 4-Ethyl-2,3-dioxo-1-piperazinyl, 4-Methyl-2,3-dioxo-1-piperazinyl, 4-Cyclopropyl-2-dioxo-1-piperazinyl, 2-Dioxomorpholinyl, 2-Dioxothiomorpholinyl; oder $-(CH_2)_nCOOR^6$ worin n=0-4 und R^3 ausgewählt ist aus Wasserstoff; gerader oder verzweigter (C_1-C_3)-Alkylgruppe, ausgewählt aus Methyl, Ethyl, n-Propyl oder 1-Methylethyl; oder (C_6-C_{10})-Arylgruppe, ausgewählt aus Phenyl, α-Naphthyl oder β-Naphthyl; R^7 ist ausgewählt aus Wasserstoff; gerader oder verzweigter (C_1-C_3)-Alkylgruppe, ausgewählt aus Methyl, Ethyl, n-Propyl oder 1-Methylethyl; (C_6-C_{10})-Arylgruppe, ausgewählt aus Phenyl, α-Naphthyl oder β-Naphthyl; (C_7-C_9)-Aralkylgruppe, wie Benzyl, 1-Phenylethyl, 2-Phenylethyl oder Phenylpropyl; eine Heterocyclus-Gruppe, ausgewählt aus einem 5-gliedrigen aromatischen oder gesättigten Ring mit einem N-, O-, S- oder Se-Heteroatom, gegebenenfalls mit einem daran kondensierten Benzo- oder Pyrido-Ring:

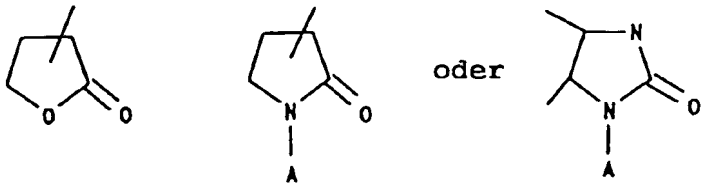


Z = N, O, S oder Se

wie Pyrrolyl, N-Methylindolyl, Indolyl, 2-Pyrrolidinyl, 3-Pyrrolidinyl, 2-Pyrrolinyl, Tetrahydrofuranyl, Furanyl, Benzofuranyl, Tetrahydrothienyl, Thienyl, Benzothienyl oder Selenazolyl, oder ein 5-gliedriger aromatischer Ring mit zwei N-, O-, S- oder Se-Heteroatomen, gegebenenfalls mit einem daran kondensierten Benzo- oder Pyrido-Ring:

Z oder Z^1 = N, O, S oder Se

wie Imidazolyl, Pyrazolyl, Benzimidazolyl, Oxazolyl, Benzoxazolyl, Indazolyl, Thiazolyl, Benzothiazolyl, 3-Alkyl-3H-imidazo-[4,5-b]pyridyl oder Pyridylimidazolyl, oder ein 5-gliedriger gesättigter Ring mit einem oder zwei N-, O-, S- oder Se-Heteroatomen und einem benachbarten angehängten O-Heteroatom:



(A ist ausgewählt aus Wasserstoff; geradem oder verzweigtem (C_1-C_4)-Alkyl; C_6-Aryl; substituiertem C_6-Aryl (Substitution ausgewählt aus Halo, (C_1-C_4)-Alkoxy, Trihalo(C_1-C_3)-Alkyl, Nitro, Amino, Cyano, (C_1-C_4)-Alkoxycarbonyl, (C_1-C_3)-Alkylamino oder Carboxy); (C_7-C_9)-Aralkylgruppe, ausgewählt aus Benzyl, 1-Phenylethyl, 2-Phenylethyl oder Phenylpropyl)

wie γ-Butyrolactam, γ-Butyrolacton, Imidazolidinon oder N-Aminoimidazolidinon, oder ein 6-gliedriger aromatischer Ring mit einem bis drei N-Heteroatomen, wie Pyridyl, Pyridazinyl, Pyrazinyl, sym-Triazinyl, asym-Triazinyl, Pyrimidinyl oder (C_1-C_3)-Alkylthiopyridazinyl, oder ein 6-gliedriger gesättigter Ring mit einem oder zwei N- O-, S- oder

Se-Heteroatomen und einem benachbarten angehängten O-Heteroatom, wie 2,3-Dioxo-1-piperazinyl, 4-Ethyl-2,3-dioxo-1-piperazinyl, 4-Methyl-2,3-dioxo-1-piperazinyl, 4-Cyclopropyl-2-dioxo-1-piperazinyl, 2-Dioxomorpholinyl, 2-Dioxothiomorpholinyl; oder $-(CH_2)_nCOCR^8$, worin n=0-4 und R^8 ausgewählt ist aus Wasserstoff, geradem oder verzweigtem (C_1-C_3)-Alkyl, ausgewählt aus Methyl, Ethyl, n-Propyl, oder 1-Methylethyl; oder (C_6-C_{10})-Aryl, ausgewählt aus Phenyl, α-Naphthyl oder β-Naphthyl; unter der Voraussetzung, daß R^6 und R^7 nicht beide Wasserstoff sein können; oder R^6 und R^7 zusammengenommen sind $-(CH_2)_2B(CH_2)_2-$, worin B ausgewählt ist aus $(CH_2)_n$ und n=0-1, -NH, $-N(C_1$-$C_3)$-Alkyl [gerade oder verzweigt], $-N(C_1$-$C_4)$-Alkoxy, Sauerstoff, Schwefel oder substituierten Substanzen gleicher Art, ausgewählt aus (L- oder D-)Prolin, Ethyl-(L- oder D-)prolinat, Morpholin, Pyrrolidin oder Piperidin; und die pharmakologisch annehmbaren organischen und anorganischen Salze oder Metallkomplexe, unter der Voraussetzung, daß, wenn R^3 und R^4 beide Wasserstoff darstellen, W dann nicht Benzylamino, 1-Imidazolyl, 1-Pyrrolyl, 1-(1,2,3-Triazolyl) oder 4-(1,2,4-Triazolyl) ist.

2. Verbindung gemäß Anspruch 1, worin R ein Halogen ist, ausgewählt aus Brom, Chlor und Jod; oder R = $-NR^1R^2$, und wenn R = $-NR^1R^2$ und R^1 = Methyl oder Ethyl, R^2 = Methyl oder Ethyl, R^3 ausgewählt ist aus Wasserstoff; R^4 ausgewählt ist aus Wasserstoff und (C_1-C_2)-Alkyl, ausgewählt aus Methyl und Ethyl; wenn R^3 nicht gleich R^4 ist, kann die Stereochemie des asymmetrischen Kohlenstoffs (d.h. des Kohlenstoffs, der den Substituenten W trägt) entweder das Razemat (DL) oder die einzelnen Enantiomere (L oder D) sein; W ist ausgewählt aus geraden oder verzweigten (C_7-C_{12})-Alkyl-monosubstituierten Aminogruppen, wobei die Substitution aus Heptyl, Octyl, Nonyl, Decyl, Undecyl, Dodecyl und den Diastereomeren und Enantiomeren dieser verzweigten Alkyl-monosubstituierten Aminogruppe ausgewählt ist; (C_2)-Fluoralkylaminogruppe, ausgewählt aus 2,2,2-Trifluorethyl und 3,3,3-Trifluorpropyl; [(C_4-C_5)-Cycloalkyl]alkyl-monosubstituierte Aminogruppe, wobei die Substitution aus (Cyclopropyl)methyl und (Cyclopropyl)ethyl ausgewählt ist; (C_3-C_4)-Alkenyl- und Alkinyl-monosubstituierte Aminogruppe, wobei die Substitution aus Allyl und Propinyl ausgewählt ist; (C_2-C_7)-Azacycloalkyl- und substituierte (C_2-C_7)-Azacycloalkylgruppe, wobei die Substitution aus 4-Methylpiperidinyl, 4-Hydroxypiperidinyl und 4-(Hydroxymethyl)piperidinyl ausgewählt ist; substituierte 1-Azaoxacycloalkylgruppe, wobei die Substitution aus 2-(C_1-C_3)-Alkylmorpholinyl ausgewählt ist; [1,n]-Diazacycloalkyl- und substituierte [1,n]-Diazacycloalkylgruppe, ausgewählt aus Piperazinyl und 4-(C_1-C_3)-Alkylpiperazinyl; 1-Azathiacycloalkyl- und substituierte 1-Azathiacycloalkylgruppe, ausgewählt aus Thiomorpholinyl und 2-(C_1-C_3)-Alkylthiomorpholinyl; (Heterocyclus-)Methylaminogruppe, ausgewählt aus 2- oder 3-Thienylmethylamino und 2-, 3- oder 4-Pyridylmethylamino; 1,1-disubstituierte Hydrazingruppe, ausgewählt aus 1,1-Dimethylhydrazin und N-Aminopiperidinyl; [β- oder γ-(C_1-C_3)-Acylamido]alkylaminogruppe, wobei die Substitution aus 2-(Acetamido)ethyl ausgewählt ist; β- oder γ-(C_1-C_3)-Alkoxyalkylaminogruppe, wobei die Substitution aus 2-Methoxyethyl, 2-Ethoxyethyl, 2,2-Diethoxyethyl, 2-Methoxypropyl und 3-Methoxypropyl ausgewählt ist; β-, γ- oder δ-(C_2-C_4)-Hydroxyalkylamino, ausgewählt aus 4-Hydroxybutyl und 3-Hydroxypropyl; oder R^3 und W zusammengenommen sind ausgewählt aus $-(CH_2)_n(R^5)N-$, n = 3, und R^5 ist ausgewählt aus Wasserstoff und Trifluoracetyl; R^6 ist ausgewählt aus Wasserstoff; gerader oder verzweigter (C_1-C_3)-Alkylgruppe, ausgewählt aus Methyl, Ethyl, n-Propyl oder 1-Methylethyl; R^7 ist ausgewählt aus Wasserstoff; gerader oder verzweigter (C_1-C_3)-Alkylgruppe, ausgewählt aus Methyl, Ethyl, n-Propyl oder 1-Methylethyl; unter der Voraussetzung, daß R^6 und R^7 nicht beide Wasserstoff sein können; oder R^6 und R^7 zusammengenommen sind $-(CH_2)_2B(CH_2)_2-$, worin B ausgewählt ist aus $(CH_2)_n$ und n=0-1, -NH, $-N(C_1$-$C_3)$-Alkyl [gerade oder verzweigt], $-N(C_1$-$C_4)$-Alkoxy, Sauerstoff, Schwefel oder substituierten Substanzen gleicher Art, ausgewählt aus (L- oder D-)Prolin, Ethyl-(L- oder D-)prolinat, Morpholin, Pyrrolidin oder Piperidin; und die pharmakologisch annehmbaren organischen und anorganischen Salze oder Metallkomplexe.

3. Verbindung gemäß Anspruch 1 oder 2, worin diese Salze oder Komplexe umfassen: Hydrochlorid, Hydrobromid, Hydrojodid, Phosphat, Nitrat, Sulfat, Acetat, Benzoat, Citrat, Cystein, Fumarat, Glycolat, Maleat, Succinat, Tartrat, Alkylsulfonat, Arylsulfonat, Aluminium, Calcium, Eisen, Magnesium oder Mangan.

4. Verbindung gemäß Anspruch 1,

[4S-(4alpha,12aalpha)]-9-[[[(Cyclopropylmethyl)amino]-acetyl]amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid-dihydrochlorid,

[4S-(4alpha,12aalpha)]-9-[[[(2,2-Diethoxyethyl)amino]-acetyl]amino]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid-dihydrochlorid;

[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,-12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[2-(methoxyethyl)-amino]acetyl]amino]-1,11-dioxo-2-naphthacencarboxamid-dihydrochlorid;

[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,-12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(2-propenylamino)acetyl]amino]-2-naphthacencarboxamid-dihydrochlorid,

[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,-12a-octahydro-3,10,12,12a-tetrahydroxy-

9-[[(3-methoxypropyl)-amino]acetyl]amino]-1,11-dioxo-2-naphthacencarboxamid-dihydrochlorid;
[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-thiomorpholinacetamid-dihydrochlorid;
[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-methyl-1-piperidinacetamid-dihydrochlorid;
[7S-(7alpha,10aalpha)]-N-[9-(Aminocarbonyl)-4,7-bis(dimethylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-2-naphthacenyl]-4-methyl-1-piperazinacetamid-dihydrochlorid;
[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-9-[[(heptylamino)acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamid-dihydrochlorid;
[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,-12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(undecylamino)acetyl]amino]-2-naphthacencarboxamid-dihydrochlorid;
[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,-12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(2-pyridinylmethyl)amino]acetyl]amido]-2-naphthacencarboxamid-dihydrochlorid;
[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,-12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[(2-hydroxyethyl)-amino]acetyl]amino]-1,11-dioxo-2-naphthacencarboxamid-monohydrochlorid;
[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,-12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[(2-hydroxyethyl)-methylamino]acetyl]amino-1,11-dioxo-2-naphthacencarboxamid;
[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,-12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[(4-(hydroxybutyl)-amino]acetyl]amino]-1,11-dioxo-2-naphthacencarboxamid;
[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,-12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[2,2,2-trifluorethyl)amino]acetyl]amino]-2-naphthacencarboxamid;
[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,-12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[[2-(1-piperidinyl)ethyl]amino]acetyl]amino]-2-naphthacencarboxamid;
[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,-12a-octahydro-3,10,12,12a-tetrahydroxy-9-[[[methyl-2-propinylamino]acetyl]amino]-1,11-dioxo-2-naphthacencarboxamid;
[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,-12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[(1-piperidinylamino)acetyl]amino]-2-naphthacencarboxamid; oder
[4S-(4alpha,12aalpha)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,-12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[[[(phenylmethoxy)amino]acetyl]amino]-2-naphthacencarboxamid.

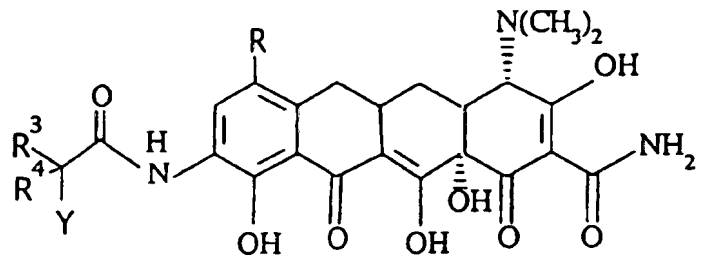
5. Verbindung gemäß Anspruch 1 zur Verwendung in einem Verfahren zur Vorbeugung oder Bekämpfung von Bakterieninfektionen bei wärmblütigen Tieren.

6. Pharmazeutische Zusammensetzung von Material, die eine pharmakologisch wirksame Menge einer Verbindung gemäß Anspruch 1 in Kombination mit einem pharmazeutisch annehmbaren Träger umfaßt.

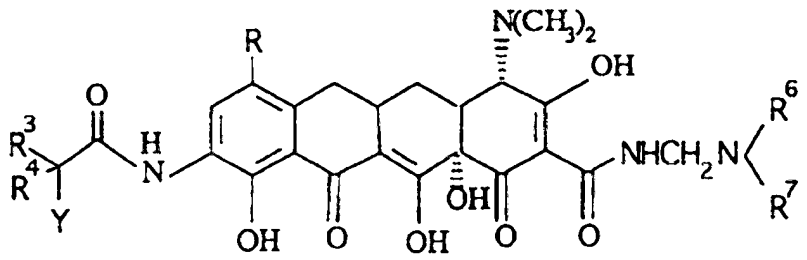
7. Veterinäre Zusammensetzung, welche eine pharmakologisch wirksame Menge einer Verbindung gemäß Anspruch 1 und einen pharmazeutisch annehmbaren Träger umfaßt.

8. Verbindung gemäß Anspruch 1 zur Verwendung in einem Verfahren zur Vorbeugung, Behandlung oder Bekämpfung von Bakterieninfektionen bei warmblütigen Tieren, die von Bakterien mit TetM- und TetK-resistenten Determinanten verursacht werden.

9. Verfahren zur Herstellung einer Verbindung der Formel I gemäß Anspruch 1, welches umfaßt: Umsetzung eines korrespondierenden 9-[(Haloacyl)amid]-7-(substituiert)-6-demethyl-6-deoxytetracyclins oder eines organischen oder anorganischen Salzes oder Metallkomplexes der Formel



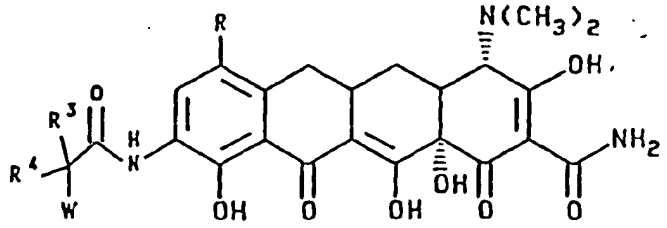
oder

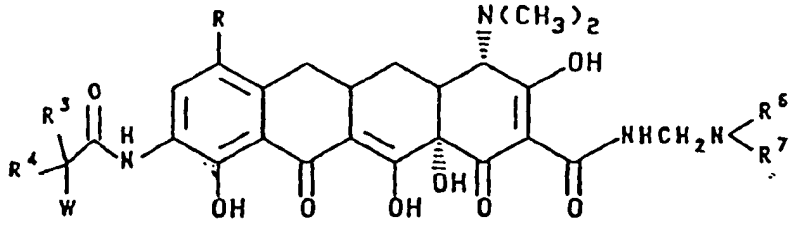


worin Y Chlor, Brom, Fluor oder Jod ist; mit einem Nucleophilen der Formel WH, worin W wie in Anspruch 1 definiert ist, in einem polar-aprotischen Lösungsmittel und in einer inerten Atmosphäre.

Revendications

1. Composé de formule :





dans lequel :
R est un atome d'halogène sélectionné parmi le brome, le chlore, le fluor et l'iode; ou bien R est un groupe $-NR^1R^2$ et, lorsque R est un groupe $-NR^1R^2$ et que R^1 est de l'hydrogène,
R^2 est l'un des groupes méthyle, éthyle, n-propyle, 1-méthyléthyle, n-butyle, 1-méthylpropyle ou 1,1-diméthyléthyle;
et lorsque R^1 est un groupe méthyle ou éthyle,
R^2 est l'un des groupes méthyle, éthyle, n-propyle, 1-méthyléthyle, n-butyle, 1-méthylpropyle ou 2-méthylpropyle;
et lorsque R' est un groupe n-propyle,
R^2 est l'un des groupes n-propyle, 1-méthyléthyle, n-butyle, 1-méthylpropyle ou 2-méthylpropyle;
et lorsque R^1 est un groupe 1-méthyléthyle,
R^2 est l'un des groupes n-butyle, 1-méthylpropyle ou 2-méthylpropyle;
et, lorsque R^1 est un groupe n-butyle,
R^2 est l'un des groupes n-butyle, 1-méthylpropyle ou 2-méthylpropyle;
et lorsque R^1 est un groupe 1-méthylpropyle,
R^2 est un groupe 2-méthylpropyle;
R^3 est sélectionné parmi l'hydrogène, un groupe alkyle en C_4-C_6 linéaire ou ramifié sélectionné parmi les groupes

butyle, isobutyle, pentyle, hexyle, heptyle et octyle;
un groupe α-mercaptoalkyl en C_1-C_4 sélectionné parmi les groupes mercaptométhyle, α-mercaptoéthyle, α-mercapto-1-méthyléthyle et α-mercaptopropyle; un groupe α-hydroxyalkyle en C_1-C_4 sélectionné parmi les groupes hydroxyméthyle, α-hydroxyéthyle, α-hydroxy-1-méthyléthyle et α-hydroxypropyle;
un groupe carboxyalkyle en C_1-C_6; un groupe aryle en C_6-C_{10} sélectionné parmi les groupes phényle, α-naphtyle et β-naphtyle; un groupe aryle substitué en C_6-C_{10} (le substituant étant sélectionné parmi les groupes hydroxy, un atome d'halogène, les groupes alcoxy en C_1-C_4, trihaloalkyle en C_1-C_3, nitro, amino, cyano, alcoxy (C_1-C_4) carbonyle, alkyl (C_1-C_3 amino et carboxy); un groupe aralkyle en C_7-C_9 sélectionné parmi les groupes benzyle, 1-phényléthyle, 2-phényléthyle et phénylpropyle; un groupe aralkyle en C_7-C_9 substitué (le substituant étant sélectionné parmi les groupes halo, alkyle en C_1-C_4, nitro, hydroxy, amino, alkyl (C_1-C_4) amino mono- ou disubstitué, alcoxy en C_1-C_4, alkyl (C_1-C_4) sulfonyle, cyano et carboxy);
R^4 est sélectionné parmi un atome d'hydrogène et un groupe alkyle en C_1-C_6 sélectionné parmi les groupes méthyle, éthyle, propyle, isopropyle, butyle, isobutyle, pentyle et hexyle;
lorsque R^3 n'est pas égal à R^4, la stéréochimie du carbone asymétrique (c'est-à-dire le carbone portant le substituant W) peut être le mélange racémique (DL) ou les énantiomères individuels (L ou D);
W est sélectionné parmi un groupe hydroxylamino; un groupe amino monosubstitué par un groupe alkyle linéaire ou ramifié en C_7-C_{12} (le substituant étant sélectionné parmi les groupes heptyle, octyle, nonyle, décyle, undécyle, dodécyle) et les diastéréomères et les énantiomères dudit groupe amino monosubstitué par un groupe alkyle ramifié; un groupe fluoroalkylamino linéaire ou ramifié en C_1-C_4 sélectionné parmi les groupes trifluorométhyle, 2,2,2-trifluoréthyle, 3,3,3-trifluoropropyle, 3,3,3,2,2-pentafluoropropyle, 2,2-difluoropropyle, 4,4,4-trifluorobutyle et 3,3-difluorobutyle; un groupe amino monosubstitué par un groupe cycloalkyl (C_4-C_{10}) alkyle (le substituant étant sélectionné parmi les groupes (cyclopropyl)méthyle, (cyclopropyl) éthyle, (cyclobutyl)méthyle, (trans-2-méthylcyclopropyl)méthyle et (cis-2-méthylcyclobutyl) méthyle; un groupe amino monosubstitué par des groupes alcényle et alcynyle en C_3-C_{10} (le substituant étant sélectionné parmi les groupes allyle, 3-butényle, 2-butényle (cis ou trans), 2-pentényle, propynyle, 4-octényle, 2,3-diméthyl-2-butényle, 3-méthyl-2-butényle, 2-cyclopenténylo et 2-cyclohexényle); un groupe aralkyl (C_7-C_{10}) amino (le substituant étant sélectionné parmi les groupes benzyle, 2-phényléthyle, 1-phényléthyle, 2-(naphtyl)méthyle, 1-(naphtyl)méthyle et phénylpropyle);
un groupe amino monosubstitué par un groupe aryle en C_6-C_{10} substitué (le substituant étant sélectionné parmi les groupes acyle en C_1-C_5, acyl (C_1-C_5) amino, alkyle en C_1-C_4, alkyl (C_1-C_8) amino mono- ou disubstitué, alcoxy en C_1-C_4, alcoxy (C_1-C_4) carbonyle, alkyl (C_1-C_4) sulfonyle, amino, carboxy, cyano, un atome d'halogène, les groupes hydroxy, nitro et trihaloalkyle en (C_1-C_3); un groupe alkylamino disubstitué symétrique linéaire ou ramifié (le substituant étant sélectionné parmi les groupes dibutyle, diisobutyle, di-sec-butyle, dipentyle, diisopentyle, di-sec-pentyle, dihexyle, diisohexyle et di-sec-hexyle); un groupe cycloalkyl (C_6-C_{14}) amino disubstitué symétrique (le substituant étant sélectionné parmi les groupes dicyclopropyle, dicyclobutyle, dicyclopentyle, di(dicyclopropyl) méthyle, dicyclohexyle et dicycloheptyle);
un groupe alkyl (C_3-C_{14}) amino disubstitué dissymétrique linéaire ou ramifié, dans lequel le nombre total d'atomes de carbone dans la substitution est supérieur à 14; un groupe cycloalkyl (C_4-C_{14}) amino disubstitué dissymétrique dans lequel le nombre total d'atomes de carbone dans la substitution n'est pas supérieur à 14; un groupe azacycloalkyle en C_2-C_8 et un groupe azacycloalkyle en C_2-C_8 substitué (le substituant étant sélectionné parmi les groupes 4-méthylpipéridinyle, 4-hydroxypipéridinyle, 4-(hydroxyméthyl)pipéridinyle, 4-(aminométhyl)pipéridinyle, cis-3,4-diméthylpyrrolidinyle, trans-3,4-diméthylpyrrolidinyle, 2-azabicyclo [2.1.1]hex-2-yle, 5-azabicyclo[2.1.1] hex-5-yle, 2-azabicyclo[2.2.1]hept-2-yle, 7-azabicyclo[2.2.1]-hept-7-yle, 2-azabicyclo[2.2.2]oct-2-yle et les diastéréomères et les énantiomères dudit groupe azacycloalkyle en C_2-C_8 et du groupe azacycloalkyle en C_2-C_8 substitué); un groupe 1-azaoxacycloalkyle substitué (le substituant étant sélectionné parmi les groupes 2-alkyl (C_1-C_3) morpholinyle, 3-alkyl (C_1-C_3) isoxazolidinyle, tétrahydrooxazinyle et 3,4-dihydrooxazinyle; un groupe [1,n]-diazacycloalkyle et un groupe [1,n]-diazacycloalkyle substitué sélectionnés parmi les groupes pipérazinyle, 2-alkyl (C_1-C_3) pipérazinyle, 4-alkyl (C_1-C_3) pipérazinyle, 2,4-diméthylpipérazinyle, 4-alcoxy (C_1-C_3) pipérazinyle, 4-aryloxy (C_6-C_{10}) pipérazinyle, 4-hydroxypipérazinyle, 2,5-diazabicyclo[2.2.1]hept-2-yle, 2,5-diaza-5-méthylbicyclo-[2.2.1] hept-2-yle, 2,3-diaza-3-méthylbicyclo[2.2.2]oct-2-yle, 2,5-diaza-5,7-diméthyl-bicyclo[2.2.2]oct-2-yle, et les diastéréomères ou les énantiomères desdits groupes [1,n]-diazacycloalkyle et [1,n]-diazacycloalkyle substitué; un groupe 1-azathia-cycloalkyle et un groupe 1-azathiacycloalkyle substitué sélectionné parmi les groupes thiomorpholinyle, 2-alkyl (C_1-C_3) thiomorpholinyle et 3-cycloalkyl (C_3-C_6) thiomorpholinyle; un groupe N-azolyle et un groupe N-azolyle substitué sélectionnés parmi les groupes 1-imidazolyle, 2-alkyl (C_1-C_3)-1-imidazolyle, 3-alkyl (C_1-C_3)-1-imidazolyle, 1-pyrrolyle, 2-alkyl (C_1-C_3)-1-pyrrolyle, 3-alkyl (C_1-C_3)-1-pyrrolyle, 1-pyrazolyle, 3-alkyl (C_1-C_3)-1-pyrazolyle, indolyle, 1-(1,2,3-triazolyle), 4-alkyl (C_1-C_3)-1-(1,2,3-triazolyle), 5-alkyl (C_1-C_3)-1-(1,2,3-triazolyle 4-(1,2,4-triazolyle), 1-tétrazolyle, 2-tétrazolyle et benzimidazolyle; un groupe amino à hétérocycle, ledit hétérocycle étant sélectionné parmi les groupes 2- ou 3-furanyle, 2- ou 3-thiényle, 2-, 3- ou 4-pyridyle, 2- ou 5-pyridazinyle, 2-pyrazinyle, 2-(imidazolyle), (benzimidazolyle) et (benzothiazolyle); un groupe amino à hétérocycle substitué (le

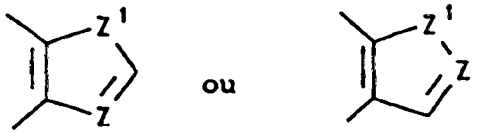
substituant étant sélectionné parmi les groupes alkyle en C_1-C_6 linéaires ou ramifiés); un groupe méthylamino à hétérocycle sélectionné parmi les groupes 2- ou 3-furylméthylamino, 2- ou 3-thiénylméthylamino, 2-, 3- ou 4-pyridylméthylamino, 2- ou 5-pyridazinylméthylamino, 2-pyrazinylméthylamino, 2-(imidazolyl)méthylamino, (benzimidazolyl)méthylamino et (benzothiazolyl)méthylamino et ledit groupe méthylamino à hétérocycle substitué (le substituant étant sélectionné parmi les groupes alkyle en C_1-C_6 linéaires ou ramifiés); un groupe carboxyalkyl (C_2-C_4) amino sélectionné parmi l'acide aminoacétique, l'acide α-aminopropionique, l'acide β-aminopropionique, l'acide α-aminobutyrique, l'acide β-aminobutyrique et les énantiomères dudit groupe carboxyalkyle (C_2-C_4) aminocarboxy; un groupe hydrazino 1,1-disubstitué sélectionné parmi les groupes 1,1-diméthylhydrazino, N-aminopipéridinyle, 1,1-diéthylhydrazino et N-aminopyrrolidinyle; un groupe alcoxy (C_1-C_4) amino (le substituant étant sélectionné parmi les groupes méthoxy, éthoxy, n-propoxy, 1-méthyléthoxy, n-butoxy, 2-méthylpropoxy et 1,1-diméthyléthoxy; un groupe cycloalcoxy (C_3-C_8) amino sélectionné parmi les groupes cyclopropoxy, trans-1,2-diméthylcyclopropoxy, cis-1,2-diméthylcyclopropoxy.

cyclobutoxy, cyclopentoxy, cyclohexoxy cycloheptoxy, cyclooctoxy, bicyclo[2.2.1]hept-2-yloxy, bicyclo[2.2.2]oct-2-yloxy et les diastéréomères et les énantiomères dudit groupe cycloalcoxy (C_3-C_8) amino; un groupe aryloxy (C_6-C_{10}) amino sélectionné parmi les groupes phénoxyamino, 1-naphtyloxyamino et 2-naphtyloxyamino; un groupe arylacoxy (C_7-C_{11}) amino (le substituant étant sélectionné parmi les groupes benzyloxy, 2-phényléthoxy, 1-phényléthoxy, 2-(naphtyl)méthoxy, 1-(naphtyl)méthoxy et phénylpropoxy; un groupe [β ou γ-acyl (C_1-C_3) amido]alkylamino (le substituant étant sélectionné parmi les groupes 2-(formamido)éthyle, 2-(acétamido)éthyle, 2-(propionylamido)éthyle, 2-(acétamido-)propyle, 2-(formamido)propyle, et les énantiomères dudit groupe [β ou γ-acyl (C_1-C_3) amido]alkylamino); un groupe β ou γ-alcoxyalkyl (C_1-C_3) amino (le substituant étant sélectionné parmi les groupes 2-méthoxyéthyle, 2-éthoxyéthyle, 2,2-diéthoxyéthyle 2-méthoxypropyle, 3-méthoxypropyle, 3-éthoxypropyle, 3,3-diéthoxypropyle, et les énantiomères dudit groupe β ou γ-alkoxyalkyl (C_1-C_3) amino; un groupe β, γ ou δ-hydroxyalkyl (C_2-C_4) amino (le substituant étant sélectionné parmi les groupes 2-hydroxyéthyle, 2-hydroxypropyle, 3-hydroxypropyle et 4-hydroxybutyle);

ou bien R^3 et W, pris conjointement, sont sélectionnés parmi -$(CH_2)_n(R^5)N$- (n = 3 - 4), et -$CH_2CH(OH)CH_2(R^5)N$- formules dans lesquelles R^5 est sélectionné parmi un atome d'hydrogène et un groupe acyle en C_1-C_3, le groupe acyle étant sélectionné parmi les groupes formyle, acétyle, propionyle et haloacyle en C_2-C_3 sélectionné parmi les groupes chloracétyle, bromacétyle, trifluoracétyle, 3,3,3-trifluoropropionyle et 2,3,3-trifluoropropionyle; R^6 est sélectionné parmi un atome d'hydrogène; un groupe alkyle en C_1-C_3 linéaire ou ramifié sélectionné parmi les groupes méthyle, éthyle, n-propyle ou 1-méthyléthyle; un groupe aryle en C_6-C_{10} sélectionné parmi les groupes phényle, α-naphtyle ou β-naphtyle; un groupe aralkyle en C_7-C_9 tel que les groupes benzyle, 1-phényléthyle, 2-phényléthyle ou phénylpropyle; un groupe hétérocyclique sélectionné parmi un noyau aromatique ou saturé à 5 atomes avec un hétéroatome N, O, S ou Se ayant facultativement un noyau benzo ou pyrido qui est fusionné avec lui :

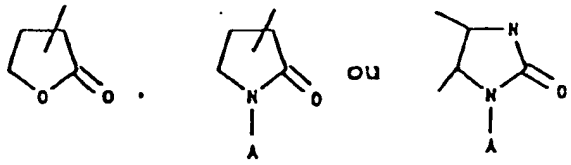
Z = N, O, S ou Se

notamment les groupes pyrrolyle, N-méthylindolyle, indolyle, 2-pyrrolidinyle, 3-pyrrolidinyle, 2-pyrrolinyle, tétrahydrofuranyle, furanyle, benzofuranyle, tétrahydrothiényle, thiényle, benzothiényle ou sélénazolyle, ou un noyau aromatique à 5 atomes avec deux hétéroatomes N, O, S ou Se qui ont facultativement un noyau benzo ou pyrido qui est fusionné avec eux :



Z ou Z^1 = N, O, S ou Se

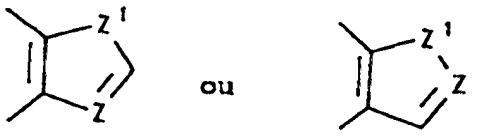
notamment les groupes imidazolyle, pyrazolyle, benzimidazolyle, oxazolyle, benzoxazolyle, indazolyle, thiazolyle, benzothiazolyle, 3-alkyl-3H-imidazo[4,5-b] pyridyle ou pyridylimidazolyle, ou un noyau saturé à 5 atomes ayant un ou deux hétéroatomes N, O, S ou Se et un hétéroatome O adjacent attaché :



(A est sélectionné parmi un atome d'hydrogène; un groupe alkyle en C_1-C_4 linéaire ou ramifié; un groupe aryle en C_6; un groupe aryle en C_6 substitué (le substituant étant sélectionné parmi les groupes halo, alcoxy en C_1-C_4, trihaloalkyle en C_1-C_3, nitro, amino, cyano, alcoxy (C_1-C_4) carbonyle, alkyl (C_1-C_3) amino ou carboxy) ; un groupe aralkyle en C_7-C_9 sélectionné parmi les groupes benzyle, 1-phényléthyle, 2-phényléthyle ou phénylpropyle)
tels que le γ-butyrolactame, la γ-butyrolactone, l'imidazolidinone ou la N-aminoimidazolidinone, ou un noyau aromatique à six atomes avec un à trois hétéroatomes N, notamment les groupes pyridyle, pyridazinyle, pyrazinyle, triazinyle symétrique, triazinyle asymétrique, pyrimidinyle ou alkyl (C_1-C_3) thiopyridazinyle, ou un noyau saturé à six atomes avec un ou deux hétéroatomes N, O, S ou Se et un hétéroatome O adjacent attaché, notamment les groupes 2,3-dioxo-1-pipérazinyle, 4-éthyl-2,3-dioxo-pipérazinyle, 4-méthyl-2,3-dioxo-1-pipérazinyle, 4-cyclopropyl-2-dioxo-1-pipérazinyle, 2-dioxomorpholinyle, 2-dioxo-thiomorpholinyle; ou $-(CH_2)_nCOOR^8$, où n est égal à 0-4 et R^8 est sélectionné parmi un atome d'hydrogène; un groupe alkyle en C_1-C_3 linéaire ou ramifié sélectionné parmi les groupes méthyle, éthyle, n-propyle ou 1-méthyléthyle; ou un groupe aryle en C_6-C_{10} sélectionné parmi les groupes phényle, α-naphtyle ou β-naphtyle;
R^7 est sélectionné parmi un atome d'hydrogène, un groupe alkyle en C_1-C_3 linéaire ou ramifié sélectionné parmi les groupes méthyle, éthyle, n-propyle ou 1-méthyléthyle; un groupe aryle en C_6-C_{10} sélectionné parmi les groupes phényle, α-naphtyle ou β-naphtyle; un groupe aralkyle en C_7-C_9 tel que l'un des groupes benzyle, 1-phényléthyle, 2-phénylèthyle ou phénylpropyle; un groupe hétérocyclique sélectionné parmi un noyau aromatique ou saturé à 5 atomes avec un hétéroatome N, O, S ou Se ayant facultativement un noyau benzo ou pyrido qui est fusionné avec lui :

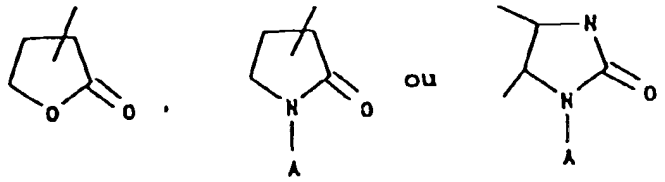
Z = N, O, S ou Se

notamment les groupes pyrrolyle, N-méthylindolyle, indolyle, 2-pyrrolidinyle, 3-pyrrolidinyle, 2-pyrrolinyle tétrahydrofuranyle, furanyle, benzofuranyle, tétrahydrothiénylo, thiénylo, benzothiényle ou sélénazolyle; ou un noyau aromatique à 5 atomes avec deux hétéroatomes N, O, S ou Se ayant facultativement un noyau benzo ou pyrido qui est fusionné avec eux :



Z ou Z^1 = N, O, S ou Se

notamment les groupes imidazolyle, pyrazolyle, benzimidazolyle, oxazolyle, benzoxazolyle, indazolyle, thiazolyle, benzothiazolyle, 3-alkyl-3H-imidazo[4,5-b] pyridyle ou pyridylimidazolyle, ou un noyau saturé à 5 atomes avec un ou deux hétéroatomes N, O, S ou Se et un hétéroatome adjacent attaché :



(A est sélectionné parmi un atome d'hydrogène; un groupe alkyle en C_1-C_4 linéaire ou ramifié; un groupe aryle en C_6; un groupe aryle en C_6 substitué (le substituant étant sélectionné parmi les groupes halo, alcoxy en C_1-C_4, trihaloalkyle en C_1-C_3, nitro, amino, cyano, alcoxy (C_1-C_4) carbonyle, alkyl (C_1-C_3) amino ou carboxy) ; un groupe aralkyle en C_7-C_9 sélectionné par les groupes benzyle, 1-phényléthyle, 2-phényléthyle ou phénylpropyle, notamment le γ-butyrolactame, la γ-butyrolactone, l'imidazolidinone ou la N-aminoimidazolidinone, ou un noyau aromatique à six atomes avec un à trois hétéroatomes N, tels que les groupes pyridyle, pyridazinyle, pyrazinyle, triazinyle symétrique, triazinyle asymétrique, pyrimidinyle, ou un groupe alkyl (C_1-C_3) thiopyridazinyle, ou encore un noyau saturé à six atomes ayant un ou deux hétéroatomes N, O, S ou Se et un hétéroatome O voisin attaché, notamment les groupes 2,3-dioxo-1-pipérazinidyle, 4-éthyl-2,3-dioxo-1-pipérazinyle, 4-méthyl-2,3-dioxo-1-pipérazinyle,4-cyclopropyl-2-dioxo-1-pipérazinyle, 2-dioxomorpholinyle, 2-dioxothiomorpholinyle; ou $-(CH_2)_nCOOR^8$, où n est égal à 0-4 et R^8 est sélectionné parmi un atome d'hydrogène; un groupe alkyle en C_1-C_3 linéaire ou ramifié sélectionné parmi les groupes méthyle, éthyle, n-propyle ou 1-méthyléthyle; ou un groupe aryle en C_6-C_{10} sélectionné parmi les groupes phényl, α-naphtyle ou β-naphtyle; à condition que R^6 et R^7 ne puissent être tous deux de l'hydrogène; ou bien R^6 et R^7, pris conjointement, sont un groupe $-(CH_2)_2B(CH_2)_2-$ dans lequel B est sélectionné parmi $(CH_2)_n$ et n est égal à 0-1, -NH, -N alkyle en C_1-C_3 [linéaire ou ramifié], -N alcoxy en C_1-C_4, de l'oxygène, du soufre ou des analogues substitués sélectionnés parmi la (L ou D) proline, l'éthyl (L ou D) prolinate, la morpholine, la pyrrolidine ou la pipéridine, et les sels organiques et minéraux ou des complexes métalliques acceptables au plan pharmacologique, à condition que, lorsque R^3 et R^4 représentent tous deux un atome d'hydrogène, W soit autre que l'un des groupes benzylamino, 1-imidazolyle, 1-pyrrolyle, 1-(1,2,3-triazolyle) ou 4(1,2,4-triazolyle).

2. Composé selon la revendication 1, dans lequel :
R est un atome d'halogène choisi parmi le brome, le chlore et l'iode; ou R est un groupe $-NR^1R^2$
et, lorsque R est un groupe NR^1R^2 et que R^1 est un groupe méthyle ou éthyle,
R^2 est un groupe méthyle ou éthyle,
R^3 est un atome d'hydrogène,
R^4 est sélectionné parmi un atome d'hydrogène et un groupe alkyle en C_1-C_2 sélectionné parmi les groupes méthyle et éthyle;
lorsque R^3 n'est pas égal à R^4, la stéréochimie du carbone asymétrique (c'est-à-dire du carbone portant le substituant W) peut être le mélange racémique (DL) ou l'un des énantiomères individuels (L ou D);
W est sélectionné parmi un groupe amino monosubstitué par un groupe alkyle linéaire ou ramifié en C_7-C_{12} (le substituant étant sélectionné parmi les groupes heptyle, octyle, nonyle, décyle, undécyle, dodécyle, et les diastéréomères et les énantiomères dudit groupe amino monosubstitué par un groupe alkyle ramifié; un groupe fluoroalkylamino en C_2 sélectionné parmi les groupes 2,2,2-trifluoréthyle et 3,3,3-trifluoropropyle;
un groupe amino monosubstitué par un groupe [cycloalkyl (C_4-C_5)] (le substituant étant sélectionné parmi les groupes (cyclopropyl)méthyle et (cyclopropyl)éthyle); un groupe amino monosubstitué par des groupes alcényle et alcinyle en C_3-C_4 (le substituant étant sélectionné parmi les groupes allyle et propynyle); un groupe azacycloalk-

yle en C_2-C_7 et un groupe azacycloalkyle en C_2-C_7 substitué sélectionné parmi les groupes 4-méthylpipéridinyle, 4-hydroxypipéridinyle et 4-(hydroxyméthyl)pipéridinyle; un groupe 1-azaoxacycloalkyle substitué (le substituant étant sélectionné parmi les groupes 2-alkyl (C_1-C_3) morpholinyle); un groupe [1,n]-diazacycloalkyle et un groupe [1,n]-diazacycloalkyle substitué sélectionné parmi les groupes pipérazinyle et 4-alkyl (C_1-C_3) pipérazinyle; un groupe 1-azathiacycloalkyle et un groupe 1-azathiacycloalkyle substitué sélectionné parmi les groupes thiomorpholinyle et 2-alkyl (C_1-C_3) thiomorpholinyle; un groupe méthylamino à hétérocycle sélectionné parmi les groupes 2- ou 3-thiénylméthylamino et 2-, 3- ou 4-pyridylméthylamino; un groupe hydrazino 1,1-disubstitué sélectionné parmi les groupes 1,1-diméthylhydrazino et N-amino-pipéridinyle; un groupe [β ou γ-acylamido (C_1-C_3)] alkylamino (le substituant étant sélectionné parmi le groupe 2-(acétamido)éthyle); un groupe β ou γ-alcoxyalkyl (C_1-C_3) amino (le substituant étant sélectionné parmi les groupes 2-méthoxyéthyle, 2-éthoxyéthyle, 2,2-diéthoxyéthyle, 2-méthoxypropyle et 3-méthoxypropyle); un groupe β, γ ou δ-hydroxyalkyl (C_2-C_4) amino sélectionné parmi les groupes 4-hydroxybutyle et 3-hydroxypropyle; ou R^3 et W, pris conjointement, sont sélectionnés parmi $-(CH_2)_n(R^5)N-$, où n est égal à 3 et R^5 est sélectionné parmi un atome d'hydrogène et un groupe trifluoracétyle;
R^6 est sélectionné parmi un atome d'hydrogène; un groupe alkyle en C_1-C_3 linéaire ou ramifié sélectionné parmi les groupes méthyle, éthyle, n-propyle ou 1-méthyléthyle;
R^7 est sélectionné parmi un atome d'hydrogène; un groupe alkyle en C_1-C_3 linéaire ou ramifié sélectionné parmi les groupes méthyle, éthyle, n-propyle ou 1-méthyléthyle, à condition que R^6 et R^7 ne puissent être tous deux de l'hydrogène;
ou R^6 et R^7, pris conjointement, sont $-(CH_2)_2B(CH_2)_2-$ dans lequel B est sélectionné parmi $(CH_2)_n$, où n est égal à 0-1, -NH, -N-alkyle en C_1-C_3 [droit ou ramifié], -N-alcoxy en C_1-C_4, un atome d'oxygène, un atome de soufre ou des analogues substitués sélectionnés parmi la (L ou D) proline, l' éthyl (L ou D) prolinate, la morpholine, la pyrrolidine ou la pipéridine; et les sels organiques et minéraux ou les complexes métalliques acceptables au plan pharmacologique.

3. Composé selon la revendication 1 ou 2, dans lequel lesdits sels ou complexes comprennent l'acide chlorhydrique, l'acide bromhydrique, l'acide iodhydrique, l'acide phosphorique, l'acide nitrique, les sulfates, les acétates, les benzoates, les citrates, la cystéine, les fumarates, les glycolates, les maléates, les succinates, les tartrates, les alkylsulfonates, les arylsulfonates, l'aluminium, le calcium, le fer, le magnésium ou le manganèse.

4. Composé selon la revendication 1,

dichlorhydrate de [4S-(4alpha,12aalpha)]-9-[[(cyclopropylméthyl)amino]acétyl]amino]-4,7-bis(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide;
dichlorhydrate de [4S-(4alpha, 12aalpha])-9-[[[(2,2-diéthoxyéthyl)amino]acétyl]amino]-4,7-bis(diméthylamino)-1,4,4a,5,5A,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide;
dichlorhydrate de [4S-(4alpha,12aalpha)]-4,7-bis(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-[[[2-(méthoxyéthyl)amino]acétyl]amino]-1,11,-dioxo-2-naphtacènecarboxamide;
dichlorhydrate de [4S-(4alpha,12aalpha)]-4,7-bis(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-9-[[(2-propénylamino)acétyl]amino]-2-naphtacènecarboxamide;
dichlorhydrate de [4S-(4alpha,12aalpha)]-4,7-bis(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-[[[(3-méthoxypropyl)amino]acétyl]amino-1,11-dioxo-2-naphtacènecarboxamide;
dichlorhydrate de [7S-(7alpha,10aalpha)]-N-[9-(amino- carbonyl)-4,7-bis(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11,-tétrahydroxy-10,12-dioxo-2-naphtacényl]-4-thiomorpholineacétamide;
dichlorhydrate de [7S-(7alpha,10aalpha)]-N-[9-(aminocarbonyl)-4,7-bis(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-4-méthyl-1-pipéridineacétamide;
dichlorhydrate de 7[7S-(7alpha,10aalpha)]-N-[9-(aminocarbonyl)-4,7-bis(diméthylamino)-5,5a,6,6a,7,10,10a,12-octahydro-1,8,10a,11-tétrahydroxy-10,12-dioxo-2-naphtacényl]-4-méthyl-1-pipérazineacétamide;
dichlorhydrate de [4S-(4alpha.12aalpha)]-4.7-bis(diméthylamino)-9-[[(heptylamino)acétyl]amino]-1,4,4a,5,5a. 6.11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-2-naphtacènecarboxamide;
dichlorhydrate de [4S-(4alpha,12aalpha)]-4,7,-bis(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-9-[[(undécylamino)acétyl]amino]-2-naphtacènecarboxamide;
dichlorhydrate de [4S-(4alpha,12aalpha)]-4,7-bis(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-9-[[[(2-pyridinylméthyl)amino]-acétyl]amido]-2-naphtacènecarboxamide;
monochlorhydrate de [4S-(4alpha,12aalpha)]-4,7,-bis(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-[[[(2-hydroxyéthyl-)amino]acétyl]amino]-1,11-dioxo-2-naphtacènecarboxamide;
[4S-(4alpha,12aalpha)]-4,7-bis(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-[[[(2-hydroxyéthyl)méthylamino]acétyl]amino]-1,11-dioxo-2-naphtacènecarboxamide;
[4S-(4alpha,12aalpha)]-4,7-bis(diméthylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-

9-[[(4-(hydroxyéthyl)méthylamino]acetyl]amino]-1,11-dioxo-2-naphtacènecarboxamide;
[4S-(4alpha,12aalpha)]-4,7-bis(diméthylamino)-1,4,4a,5, 5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-[[(4-(hydroxybutyl)amino]acétyl]amino]-1,11-dioxo-2-naphtacènecarboxamide;
4S-(4alpha,12aalpha)]-4,7-bis(diméthylamino)-1,4,4a,5, 5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1-11-dioxo-9-[[[2,2,2-(trifluoréthyl)amino]acétyl]amino-2-naphtacènecarboxamide;
[4S-(4alpha,12aalpha)]-4,7-bis(diméthylamino)-1,4,4a,5, 5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-9-[[[[2-(1-pipéridinyl)éthyl]amino]acétyl]-amino]-2-naphtacènecarboxamide;
[4S-(4alpha,12aalpha)]-4,7-bis(diméthylamino)-1,4,4a,5, 5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-9-[[[méthyl-2-propynylamino]acétyl]amino]-1,11-dioxo-2-naphtacènecarboxamide;
[4S-(4alpha,12aalpha)]-4,7-bis(diméthylamino)-1,4,4a,5, 5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-9-[[(1-pipéridinylamino)acétyl]amino]-2-naphtacènecarboxamide, ou
[4S-(4alpha,12aalpha)]-4,7-bis(diméthylamino)-1,4,4a,5, 5a,6,11,12a-octahydro-3,10,12,12a-tétrahydroxy-1,11-dioxo-9-[[(1-phénylméthoxy)amino]acétyl]amino]-2-naphtacènecarboxamide

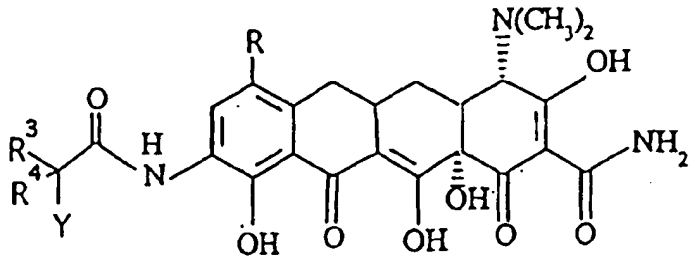
5. Composé selon la revendication 1 destiné à être utilisé dans un procédé pour la prévention ou le contrôle d'infections bactériennes chez des animaux à sang chaud.

6. Composition pharmaceutique de matière comprenant une quantité efficace au plan pharmacologique d'un composé selon la revendication 1 en association avec un véhicule acceptable au plan pharmaceutique.

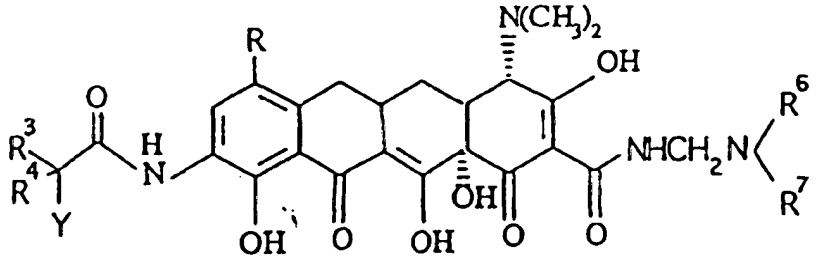
7. Composition vétérinaire qui comprend une quantité efficace au plan pharmacologique d'un composé selon la revendication 1 et d'un véhicule acceptable au plan pharmaceutique.

8. Composé selon la revendication 1 destiné à être utilisé dans un procédé pour la prévention, le traitement ou le contrôle d'infections bactériennes chez des animaux à sang chaud, dues à des bactéries ayant les déterminants de résistance TetM et TetK.

9. Procédé de production d'un composé de formule I selon la revendication 1, qui comprend l'étape de mise en réaction d'une 9-[(haloacyl)amido]-7-(substitué)-6-déméthyl-6-désoxytétracycline ou d'un sel organique ou minéral ou un complexe métallique de formule :



ou



dans laquelle Y est du chlore, du brome, du fluor ou de l'iode; avec un nucléophile de formule WH, dans laquelle W est tel que défini dans la revendication 1, dans un solvant polaire aprotique et dans une atmosphère inerte.